Australian Government

Department of Health and Ageing

Australia and New Zealand Horizon Scanning Network

ANZHSN

AN INITIATIVE OF THE NATIONAL, STATE AND TERRITORY GOVERNMENTS OF AUSTRALIA AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary Update

Screening for lung cancer utilising computed tomography (CT)

March 2010

AHTA

Adelaide Health Technology Assessment

ISBN
Publications Approval Number:

Electronic copies can be obtained from http://www.horizonscanning.gov.au

Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

DISCLAIMER: This report is based on information available at the time of research cannot be expected to cover any developments arising from subsequent improvements health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

The Commonwealth does not guarantee the accuracy, currency or completeness of the information in this report. This report is not intended to be used as medical advice and intended to be used to diagnose, treat, cure or prevent any disease, nor should it be used therapeutic purposes or as a substitute for a health professional's advice. The Commonwealth does not accept any liability for any injury, loss or damage incurred by use of or reliance the information.

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

This Horizon scanning prioritising summary was prepared by Ben Ellery, Linda Mundy and Professor Janet Hiller from the National Horizon Scanning Unit, Adelaide Health Technology Assessment, Discipline of Public Health, School of Population Health and Clinical Practice, Mail Drop DX 650 545, University of Adelaide, Adelaide, SA, 5005.

PRIORITISING SUMMARY: UPDATE 2010

REGISTER ID:	**000275**
NAME OF TECHNOLOGY:	**SCREENING FOR LUNG CANCER UTILISING COMPUTED TOMOGRAPHY (CT)**
PURPOSE AND TARGET GROUP:	**TARGETED SCREENING BY CT FOR LUNG CANCER IN ASYMPTOMATIC HIGH-RISK POPULATION GROUPS**

2010 SAFETY AND EFFECTIVENESS ISSUES:

The 2008 update reported on the initial results of a RCT conducted by Infante et al (2007). Three-year follow-up results are now available for this RCT (n=2,472) which compared patients[1] under annual clinical review for lung cancer with or without CT screening. All participants underwent baseline chest X-ray (CXR) and sputum cytology. Although a median follow-up of 33 months was reported, compliance with yearly screening was poor. In the CT arm, after initial assessment at enrolment, loss-to-follow-up was reasonable in the first year at 13 per cent, however at the CT screens performed at two, three and four years, follow-up was poor with 66, 44 and 20 per cent of patients undergoing a CT screen. Similar compliance was reported in the control arm with only 15 per cent of patients assessed at the four-year end point. The lung cancer detection rate among the CT group was considerably higher at baseline (28/1276, 2.19%) compared to the control group (8/1196, 0.67%) who underwent the same yearly medical examination with the exception of CT screening. At the end of 33 months follow-up, the lung cancer detection rate was statistically higher in the CT group 4.7 per cent (60/1276) compared to 2.8 per cent (34/1196) in the control group (p=0.016). The number of lung cancers detected at baseline, during screening and between screens (interval) in each arm is summarised in Table 1.

There was a statistically significant difference in the proportion of stage I tumours detected in the CT group compared to the control group (54 vs. 34%, p=0.004). A total of 61 tumours were detected in 60 patients in the CT group, of which 33 (54.1%) were stage I, 11 (18.03%) were stage II-IIIA and 17 (27.9%) were stage IIIB-IV. In the control group, 35 tumours were detected in 34 patients, of which 12 were stage I (34.3%), six were stage II-IIIA (17.1%) and 17 were stage IIIB-IV (48.6%). Of 46 patients diagnosed by CT in the screening group, 30 (63.8%) were found to have stage I lung cancer. Only two of the remaining thirteen interval and follow-up cases were diagnosed at stage I. Additionally, one patient was detected with stage I cancer by baseline sputum cytology. In the control group, 34 patients were diagnosed with 35 tumours. Four patients were diagnosed with a stage I tumour at baseline and a further

[1] Males aged 60 to 75 years with 20 or more pack-years smoking exposure.

eight tumours were classified as stage I in either the screening or follow-up phase. The remaining 23 tumours were classified as stage II – IV lung cancer.

Table 1 Lung cancer detected by CT and control clinical review and associated mortality after 33 months of follow up

Lung cancer detection	CT arm (n=1,276)	Control arm (n=1,196)
Total cancers detected	60/1276 (4.7%)	34/1196 (2.8%)
Baseline	28/60 (46.7%)	8/34 (23.5%)
Screening	19/60 (31.6%)	3/34 (8.8%)
Interval	10/60 (16.7%)	23/34 (67.6%)
Post-follow-up	3/60 (5.0%)	
Mortality		
Mortality of total cancers detected	20/1276 (1.57%)	20/1196 (1.67%)
Mortality of baseline cases	10/28 (35.7%)	1/34 (2.94%)
Mortality of screening cases	0/19 (0.0%)	2/3 (66.7%)
Mortality of interval + follow-up cases	10/13 (76.9%)	17/23 (73.9%)

The reported overall mortality rate due to lung cancer was similar in both the control and CT groups (1.67 vs. 1.57%). Mortality for all other causes was also similar for both groups (2.1 vs. 2.0%). In the CT group, only one of the 33 stage I patients died of lung cancer, while the remaining 19 patients who died of lung cancer were in stages II – IV. No data were provided on stage of disease and mortality in the control group.

A significantly higher proportion of invasive procedures were undertaken for patients in the CT arm (n=45) than for controls (n=20) ($p<0.0001$). Of the 45 patients who had major surgery for suspected lung cancer in the CT group, a diagnosis was confirmed in 39 cases. Consequently, 6/45 (13.3%) in the CT group had a major surgical procedure for a benign condition compared to 3/20 (15%) of the controls (Infante et al 2009) (level II screening evidence).

From this study it would appear that CT is capable of diagnosing a proportionally higher number of patients with stage I lung cancer than clinical diagnosis alone. It would be expected that an earlier diagnosis may be reflected in a better mortality outcome in the CT group when compared to clinical diagnosis alone, however there was no reported difference in mortality between the two groups in this study. Poor follow-up in both groups makes it difficult to establish a firm conclusion about the usefulness of CT screening for lung cancer and good evidence that early diagnosis improves survival is lacking.

A study reported potential health outcomes for CT screening over 15 years using the Lung Cancer Policy Model (LCPM). The LCPM is a comprehensive micro-simulation

of lung cancer development, progression, detection, treatment and survival. Using this model, a simulation representative of six US cohorts[2] compared three screening scenarios with a non-screening scenario across each fixed cohort (n=500,000×6). The three screening scenarios included current and former smokers with a minimum 20 pack-years smoking exposure; once off baseline screen in 1990; annual screening over 15 years; and bi-annual screening over 15 years. The LCPM was previously calibrated against age specific lung cancer incidence from tumour registry data. Non-smokers were included in the cohorts to generate incidence rates for the LCPM non-screening scenario representative of observed rates of lung cancer in the general population.[3] Elevated incidences in screening scenarios produced shifts to earlier stage lung cancers at the time of diagnosis.[4] This shift is in line with the higher predicted five-year lung cancer-specific survival rates from the model for bi-annual screening (60–69%) versus no screening (21–27%). However, the effect of lead-time bias in the early diagnosis of lung cancer must be taken into account, as patients may have the same mortality rates despite being diagnosed earlier in the disease pathway.[5]

Small gains in life expectancy from annual screening, dependent on age and sex, ranged from 3.4 weeks for females aged 70 years to 10.1 weeks for males aged 60 years. Life expectancy gains for bi-annual screening were only slightly better (3.9 weeks for females aged 70 years and 12 weeks for males aged 60 years). These results indicate that even among higher risk populations, CT screening for lung cancer may not offer much improvement in survival (McMahon et al 2008) (level III-2 screening evidence).

A large Japanese study recruited men aged 40-59 years (n=14,058) to investigate if the incidence of lung cancer detected by CT screening would approximate the incidence of lung cancer observed from population-based cancer registries.[6] The men were categorised by smoking history as either non-, current-, or former smokers, comprising 30.7, 47.5 and 21.8 per cent of the sample population respectively. Mean follow-up was approximately three years.

Total incidence of lung cancer among men aged 40-59 years who had undergone CT screening was 24.4 per 100,000 person-years (95% CI [13.6, 43.6]). Incidence was 15.2 (95% CI [4.2, 55.5]) in non-smokers, 31.7 (95% CI [15.4, 65.4]) in current smokers and 20.1 (95% CI [5.52, 73.4]) in former smokers. For men aged 40-49 years, no incident lung cancers were detected. This corresponds with large population-based reports of low incidence[7] among this age group, (Marugame et al 2007)

[2] Males and females aged 50, 60 and 70 years at study commencement.
[3] Non-smokers were not subjected to screening scenarios.
[4] 24–32 per cent of non-small cell lung cancers diagnosed in non-screening scenarios were stage I/II, while bi-annual screening yielded 69–79 per cent stage I/II cancers.
[5] When lead time bias occurs, a patient diagnosed earlier may appear to live longer than a patient diagnosed later, when in fact time spent living with the diagnosis is increased, not the survival time.
[6] Lung cancer incidence has been widely enumerated in Japan where chest radiography once or twice yearly is a common standard.
[7] 9.2-20.3 cases per 100,000 person years.

suggesting CT screening in this age group is not recommended. Incidence among men aged 50-59 years was 56.5 per 100,000 person-years; 36.9 (95% CI [10.1, 135]) for non-smokers, 74.8 (95% CI [36.2, 154]) for current smokers, and 42.8 (95% CI [11.7, 156]) for former smokers. Among current smokers aged 50-59 years with 40 or more pack-years smoking history, lung cancer incidence was 233.1 per 100,000 person-years (95% CI [106.8, 508.6]). The overall incidence for subjects aged 40-49 and 50-59 years in this screening study were found to correspond closely with population-based studies (Marugame et al 2007). Comparing the CT rates of 24.4 and 56.5 for the respective age groups with the population-based rates of 9.2-20.3 and 43.3-72.0 suggests CT screening is sensitive for identifying lung cancer incidence. Incidence of lung cancers was highest in men aged 50-59 years with no less than 40 pack-years smoking exposure which could make this group an optimal target for CT screening. However, Nojo et al (2009) reported only on incidence with no investigation of interventions for improved prognosis. Determination of CT screening's sensitivity to detect disease without inquiry about the effectiveness of subsequent treatments does not support the test's recommendation. Also, the total number of incident lung cancers was low (n=9)[8], resulting in incidence rates with wide confidence intervals, indicating screening recommendations require additional caution. Longer follow-up could generate more robust results. Selection bias and demographic profile of the study sample deter extrapolation of results to the general population[9] (Nojo et al 2009) (level IV screening evidence).

Baseline and annual repeat CT screening was performed for at-risk individuals[10] (n=3,352) during a four-year Toronto study. Main objectives were to determine efficacy in the detection of parenchymal nodules and diagnosis of early stage lung cancer. Baseline CT screens were positive for 600 (18%) of subjects. These individuals were recommended for follow-up CT screening in one, three or six months on the basis of tumour pathology. Participants with negative baseline results (n=2,752) were recommended for the annual repeat screen, for which 2,686 (80%) returned. From study commencement, 82 individuals were indicated for biopsy, of whom 64 were diagnosed with lung cancer by CT. Total lung cancers diagnosed were 65, with 62 CT-detected and 3 interval cases. Fifty-seven cancers were non-small cell carcinoma of which 82 per cent were at stage I or II with a resectability rate of 80 per cent. The screening procedure diagnosed early stage lung cancers with sensitivity of 87.7 per cent and specificity of 99.3 per cent. A high overall detection rate of 1.9 per cent is consistent over a ten-year period with other studies ranging between 0.4 (Sone et al 2001) and 2.7 per cent. To summarise, diagnostic yield and subsequent resections

[8] Non-smokers, current smokers and former smokers developed 2 cancers in 13,138, 7 in 22,085 and 2 in 9,929 person-years respectively.
[9] All subjects were volunteers. Authors state that factors including occupation, residence, environment, education status and age were not accounted for in the study design.
[10] Smoking history of at least 10 pack-years (range = 10–189, median = 30).

were the main results of this study, with no follow-up of survival (Henschke et al 1999; Menezes et al 2009) (level IV screening evidence).

Another case-series recruited subjects[11] (n=3,642) to evaluate the ability of CT screening to diagnose lung cancer in early stages and followed disease outcomes over three years. Of the 3,642 subjects eligible for initial screening, 3,423 went on to receive repeat screening one year later. Compliance with repeat screening was similar for men and women, 95.8 and 94.7 per cent respectively (p=0.12). A total of 1,477 (40.6% of 3,624) subjects were notified of non-calcified lung nodules at initial screening. Of the 1,477 subjects, 821 underwent additional diagnostic testing[12] before the repeat screening scheduled one year from baseline. Thirty-six (1%) underwent surgery[13] for benign disease. Sixty-nine subjects were finally diagnosed with non-small cell lung cancer of which 58 per cent were stage I with high potential for cure. Of 82 subjects who had video-assisted thorascopic surgery or thoracotomy, 28 (34%) had non-cancer outcomes. These rates of invasive surgical procedure are in line with a number of prior single-arm studies and published results of surgery for non-calcified lung nodules[14] (Miller 2008; Wilson et al 2008) (level IV screening evidence).

2010 SUMMARY OF FINDINGS:

Discrepancies in reported outcomes of patients involved in CT screening for lung cancer continue to persist. Some data show promise in the detection of early-stage lung cancers for at-risk populations, which may provide greater potential for treatment. However, issues of over-diagnosis, use of invasive procedures for benign disease, impact on survival, cost-effectiveness and appropriate target populations remain. Evidence for the effectiveness of treating lung cancer patients identified by CT screening is lacking. Furthermore, results of several RCTs (Yau et al 2007) expected to be available by 2009 remain to be published. RCTs provide the comparative evidence lacking in case series studies. Accordingly, an RCT can offer more definitive conclusions about the effectiveness of a diagnostic test such as CT screening in improving lung cancer prognosis. The only RCT available for this update was limited by substantial loss to follow-up.

2010 HEALTHPACT ACTION:

Some sources examined suggest that CT screening may be effective in diagnosing lung cancer at earlier stages than possible by chest X-ray. However, it remains unclear which populations can be considered optimal screening targets, and substantial doubts remain about gains in life expectancy from CT screening. This technology has been

[11] Males and females aged 50 to 79 years with median smoking history of 49 pack-years (range = 33–62 pack-years).
[12] CT, positron emission tomography (PET), or both.
[13] Nine thoracotomy, 21 video-assisted thorascopic surgery, two median sternotomy, four mediastinoscopy.
[14] Rates of 50 per cent in the mid-1990s and 20 per cent more recently.

previously monitored and therefore no further review by HealthPACT is required as routine scanning will identify any relevant studies published in the future.

2010 LIST OF STUDIES INCLUDED:

Total number of studies	5
Level II screening evidence	1
Level III-2 screening evidence	1
Level IV screening evidence	3

2010 REFERENCES:

Henschke, C. I., McCauley, D. I. et al (1999). 'Early Lung Cancer Action Project: overall design and findings from baseline screening', *Lancet,* 354 (9173), 99-105.

Infante, M., Cavuto, S. et al (2009). 'A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial', *Am J Respir Crit Care Med,* 180 (5), 445-453.

Marugame, T., Matsuda, T. et al (2007). 'Cancer incidence and incidence rates in Japan in 2001 based on the data from 10 population-based cancer registries', *Jpn J Clin Oncol,* 37 (11), 884-891.

McMahon, P. M., Kong, C. Y. et al (2008). 'Adopting helical CT screening for lung cancer: potential health consequences during a 15-year period', *Cancer,* 113 (12), 3440-3449.

Menezes, R. J., Roberts, H. C. et al (2009). 'Lung cancer screening using low-dose computed tomography in at-risk individuals: The Toronto experience', *Lung Cancer*.

Miller, Y. E. (2008). 'Minimizing unintended consequences of detecting lung nodules by computed tomography', *Am J Respir Crit Care Med,* 178 (9), 891-892.

Nojo, T., Imanaka, Y. et al (2009). 'Lung cancer incidence in middle-aged men estimated by low-dose computed tomography screening', *Lung Cancer,* 65 (1), 56-61.

Sone, S., Li, F. et al (2001). 'Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner', *Br J Cancer,* 84 (1), 25-32.

Wilson, D. O., Weissfeld, J. L. et al (2008). 'The Pittsburgh Lung Screening Study (PLuSS): outcomes within 3 years of a first computed tomography scan', *Am J Respir Crit Care Med,* 178 (9), 956-961.

Yau, G., Lock, M. & Rodrigues, G. (2007). 'Systematic review of baseline low-dose CT lung cancer screening', *Lung Cancer,* 58 (2), 161-170.

PRIORITISING SUMMARY UPDATE (2008)

REGISTER ID:	**000275**
NAME OF TECHNOLOGY:	**SCREENING FOR LUNG CANCER UTILISING COMPUTED TOMOGRAPHY (CT)**
PURPOSE AND TARGET GROUP:	**TARGETED SCREENING BY CT FOR LUNG CANCER IN ASYMPTOMATIC HIGH-RISK POPULATION GROUPS**

2008 EFFECTIVENESS AND SAFETY ISSUES:

The main concerns arising from the use of CT for lung cancer screening are the cost effectiveness of the procedure, the potential to over diagnose and the impact, if any, on lung cancer mortality. Since the original prioritising summary was published there have been many large studies in the area of CT-based screening for lung cancer, therefore only a selection[15] of the largest were reviewed in the preparation of this update.

A RCT which enrolled 2472[16] subjects compared CT screening over four years to a baseline chest X-ray (CXR) with subsequent clinical assessment over four years, reported a higher detection rate of lung cancers at baseline in the CT arm (2.19%) versus the CXR arm (0.67%). The stage I cancer detection rate was four times higher in the CT arm of the study, indicating a better detection of early stage lung cancer. Additionally, there was a higher resection rate in the CT arm. A higher resection rate generally means a more favourable patient prognosis versus lower resection rates in patients with more advanced, inoperable cancers. However, mortality data were not available yet and as such the primary effectiveness of CT screening cannot be judged (Infante et al 2007) (level II screening evidence).

The New York Early Lung Cancer Action Project study prospectively recruited 6,295 subjects[17]. All subjects underwent CT at baseline with a subpopulation receiving a CT scan one year later. Additionally, if results of the first CT scan were positive, subjects underwent additional CT or PET scans as part of their clinical work up. In those subjects where lung cancer was detected, a high rate[18] of early lung cancer was reported with only 9 and 15 per cent having evidence of metastasis at baseline and one-year CT scans. Overdiagnosis in this study was controlled for by investigating the

[15] The study selection criteria were: large population size, high quality study design, patient outcomes reported and longitudinal patient follow up. Studies meeting one or more of these criteria were selected over studies that did not.

[16] Male subjects, 60–74 years old, and smokers greater than 20 pack-years

[17] Both sex subjects, aged 60 years or older, had smoked for at least 10 pack-years, had no prior cancer, had not undergone chest CT in the previous 3 years, and were medically fit to undergo thoracic surgery.

[18] UK data show that only 13 per cent of lung cancer patients present with cancer that is at a resectable stage (stages IA to IIB). Metastasis to the lymph nodes is a defining factor of stage II or higher disease NHS (2006). *National Lung Cancer Audit,* National Health Service, UK..

growth of detected tumours, that is, nodules needed to demonstrate growth between CT scans for them to be classified as lung cancer. Checking the tumours for growth allows a positive diagnosis to only apply to patients with tumours that are expected to be clinically important within that patient's life expectancy. Biopsies were recommended for 134 patients with 125 (93.3%) being diagnosed as malignant. Another 24 biopsies were performed outside the study recommendations and none of these were diagnosed as lung cancer. Mortality or cost-effectiveness data were not calculated or reported (NY-ELCAP 2007) (level IV screening evidence).

A study involving general population lung cancer screening by CT, recruited 5480 subjects[19] for annual low-dose CT based screening (Sone et al 2007). Lung cancer was detected in both smokers (n=29) and non-smokers (n=28), with 63[20] cases of lung cancer being diagnosed during the time of the study and follow-up. Of these cases 60 were detected by CT, one was detected by sputum cytology but was missed by CT, and two were interval cases detected between annual CT scans. Of 57 patients who had lung cancer detected by CT and underwent surgery, 21 had bronchioloalveolar carcinoma (BAC), 24 had adenocarcinoma with mixed subtypes, 10 had non-BAC-adenocarcinoma and two had well-differentiated adenocarcinoma. The survival rate for treated patients was excellent and the long term follow-up of 59 patients with lung cancer found a 10 year survival rate of 83.1 per cent. Factors that were found to have significant correlation to survival were early stage of cancer when detected, being a non-smoker, and small size and low density of the tumour. The authors estimated the rate of overdiagnosis[21] as being 13 per cent (Sone et al 2007) (level IV screening evidence).

Another longitudinal (median follow-up 3.9 years) study involving 3,246 subjects who were current or past smokers, reported that although low-dose CT scans did increase lung cancer diagnosis and surgery, it did not reduce the risk of advanced lung cancer diagnoses or deaths resulting from lung cancer. Validated prediction models were used to generate likely numbers of diagnoses and outcomes in the study population if CT screening was not used. The actual CT diagnoses and longitudinal outcomes were compared to modelled data, which served as a form of control population. Compared to the modelled control population the authors concluded that CT based screening did not significantly impact on overall patient mortality. Cost

[19] 2969 men, 2511 women, aged 40–74, 2047 (37.4%) smokers, 393 (7.2%) ex-smokers (who have stopped smoking for more than 5 years) and 3040 (55.4%) non-smokers.

[20] It is not clear why the designation of smokers (past and present n=29) and non-smokers (n=28) was only applied to 57 patients and not the total of 63 who were diagnosed as lung cancer positive. This may be due to the fact that 57 patients had CT diagnosed cancer and underwent surgery.

[21] The overdiagnosed are those patients who despite being diagnosed with lung cancer and treated would, if left untreated, have had a higher probability of dying of other causes due to the slowly progressing nature of their lung cancer. Hence their diagnosis and treatment for lung cancer could be regarded as unnecessary as lung cancer is not likely to have caused their death.

effectiveness was not calculated (Bach et al 2007) (level IV screening evidence[22]).

There are wide discrepancies in the reported outcomes of patients in CT based lung cancer screening programs. Some of the studies presented here show promise in the early detection of lung cancers and many patients are successfully treated for these cancers. Despite this, it is not clear whether this outcome is derived from overdiagnosis and subsequent treatment of "healthy" patients, or whether this is a real benefit of advanced, early treatment. Much of the evidence published to date was generated in studies lacking control populations, blinding and randomisation. Additionally, most studies do not include cost effectiveness and many report diagnoses and treatment without mortality data. This lack of meaningful information may be rectified as several RCTs are currently underway with results expected to be reported in 2009 (Yau et al 2007).

2008 CONCLUSION:

While a large number of studies reported in the interval since the publication of the original prioritising summary, and with some promising results, the quality of the evidence has not progressed to a significant extent. There remain many questions as to the effectiveness of CT-based lung cancer screening, including overdiagnosis, the impact on mortality, cost effectiveness and which populations, if any, to screen. Several RCTs are underway and will report in the next few years.

2008 HEALTHPACT ACTION:

Monitor for further information in 24-months time.

LIST OF STUDIES INCLUDED

Total number of studies	4
Level II screening evidence	1
Level IV screening evidence	3

FEBRUARY 2008 - SOURCES OF FURTHER INFORMATION:

Bach, P. B., Jett, J. R. et al (2007). 'Computed tomography screening and lung cancer outcomes', *Jama*, 297 (9), 953-961.

Infante, M., Lutman, F. R. et al (2007). 'Lung cancer screening with spiral CT Baseline results of the randomized DANTE trial', *Lung Cancer*.

NY-ELCAP (2007). 'CT Screening for lung cancer: diagnoses resulting from the New York Early Lung Cancer Action Project', *Radiology*, 243 (1), 239-249.

Sone, S., Nakayama, T. et al (2007). 'Long-term follow-up study of a population-based 1996-1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography', *Lung Cancer*, 58 (3), 329-341.

Yau, G., Lock, M. & Rodrigues, G. (2007). 'Systematic review of baseline low-dose CT lung cancer screening', *Lung Cancer*, 58 (2), 161-170.

[22] This level of evidence was given despite the study having a pseudo-control group based on modelling of expected outcomes. Due to the many assumptions made when constructing a model, this control was not given the same weight as a true control consisting of another demographically similar population to the experimental group.

PRIORITISING SUMMARY (2007)

REGISTER ID: **000275**

NAME OF TECHNOLOGY: **SCREENING FOR LUNG CANCER UTILISING COMPUTED TOMOGRAPHY (CT)**

PURPOSE AND TARGET GROUP: **TARGETED SCREENING BY CT FOR LUNG CANCER IN ASYMPTOMATIC HIGH-RISK POPULATION GROUPS**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

☐	Yet to emerge	☐	Established
☐	Experimental	☐	Established *but* changed indication or modification of technique
☒	Investigational	☐	Should be taken out of use
☐	Nearly established		

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐	Yes	ARTG number
☐	No	
☒	Not applicable	

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United States	✓		
Europe	✓		
Japan	✓		
Israel	✓		
United Kingdom	✓		

IMPACT SUMMARY:

This prioritising summary examines recent evidence for the use of computer tomography (CT) utilised for lung cancer screening, and its applicability to the Australian setting. There is a growing interest worldwide in CT screening for lung cancer in light of evidence demonstrating reduced mortality in screened population groups.

2007 BACKGROUND

Despite improvements in the treatment and mortality rates for cancers including breast and prostate cancers, lung cancer remains the most common fatal cancer with minimal improvement in five-year survival rates during the past 30 years (Read et al 2006). As the disease does not generally cause symptoms in its early stages, lung cancer is usually detected at a late stage of development when it has spread to lymph nodes or

other sites. Detecting tumours at an early stage of disease may facilitate potentially life-saving treatment. Currently only 15-20% of lung cancers are diagnosed in early stages, and when diagnosed the disease has spread outside the lung in 15-30% of cases (Rossi et al 2005). The most effective treatment for lung cancer is surgical resection at an early stage of disease.

Lung cancer is clinically divided into two categories: non-small cell lung cancer (NSCLC), including squamous carcinoma, adenocarcinoma and large cell carcinoma, representing approximately 80% of all lung cancers, and small cell lung cancer (SCLC). The latter is known to metastasise early and is generally not considered for surgery resection (Rossi et al 2005).

Individuals considered at high risk of developing lung cancer include smokers with Chronic Obstructive Pulmonary Disease (COPD), patients with previous cancers and those with a history of asbestos exposure.

Computed tomography can detect tumours as small as 0.5cms compared to a chest X-ray which detects tumours at 3cms (Read et al 2006). However, it is important to note that smaller tumour size does not necessarily equate to an early stage cancer as each tumour has its own growth pattern and disease development. The potential benefits of introducing CT screening for lung cancer detection may be its ability to detect more early stage cancers and decrease the numbers of later stage disease.

2007 Clinical Need and Burden of Disease

Lung cancer is the leading cause of death in Australia with 7,800 new cases and 6,800 deaths each year. The overall survival rate for lung cancer in Australia is very low at 12 to 14 % (The Cancer Council Australia 2004). Despite the success of smoking cessation programs, a large number of people continue to be at high risk of lung cancer, including long-term smokers who have ceased smoking. About 50 per cent of cancers are now detected in former smokers and it is expected that the majority of future lung cancer cases will occur in this group (NCCI 2003). The 5-year survival rate among patients with Stage I lung cancer is approximately 70 per cent. This rate declines to approximately five per cent amongst patients with Stage IV lung cancer (Unger 2006).

2007 Diffusion

There is no organised screening program for lung cancer screening of asymptomatic people in Australia. Further, screening is not recommended in asymptomatic patients in general clinical practice. Lung cancer is detected in symptomatic patients in different ways including incidental chest x-ray findings resulting from persistent lung or other symptoms. Patients may be referred for CT testing to further investigate chest X-ray findings (The Cancer Council Australia 2004).

It is unlikely that routine screening by CT for lung cancer will occur in Australia in the absence of high level evidence of its benefits.

2007 COMPARATORS

In symptomatic patients, lung cancer diagnostic tests such as sputum cytology and conventional chest radiography are generally conducted in clinical practice.

Previous studies conducted in the 1970s investigated lung cancer screening based on conventional chest radiography and sputum cytology, either alone or in combination. These studies demonstrated that, although lung cancers are diagnosed earlier, there is no benefit in terms of a reduction in mortality rate following screening. This may be explained either by earlier diagnosis not having a sufficient impact on outcome, or by the screening measures, and subsequent investigations and treatment, having detrimental effects that outweigh any small benefit. As a result, routine chest radiography and sputum cytology are not recommended for screening. Despite the lack of evidence of benefit, a recent survey suggested that many doctors in Australia recommend conventional chest radiography routinely for high-risk patients (NCCI Working Group on Lung Cancer Screening 2003).

2007 EFFECTIVENESS AND SAFETY ISSUES

At the time of preparing this summary numerous studies and reviews of studies (level IV screening evidence) conducted in the late 1990s and early 2000s were identified on PUBMED that describe the effectiveness of CT in detecting early lung cancers. These studies have assessed numbers and size of detected nodules, numbers of cancers detected and their size, stage, and surgical resectability.

A recent published review reported on a number of pilot studies (level IV screening evidence) of CT screening in patient groups that are at increased risk for lung cancer, including current and former smokers. Overall, 55-85 per cent of cancers detected in baseline scans, and 60-100 per cent of cancers detected in annual follow-up scans were Stage I tumours. In contrast, only 16 per cent of cancers that are diagnosed in the course of routine clinical care in the United States are Stage I (Mulshine and Sullivan 2005).

The study with the longest follow-up data of those included in the above review was conducted by the Mayo Clinic reports on 5-year experience with CT screening for lung cancer (level IV screening evidence) (Swensen et al 2005). The authors reported the results of five consecutive annual CT screenings of 1,520 asymptomatic individuals aged 50 years or older who had smoked ≥20 packets per year (Swensen et al 2005). In a total of 1520 people 61% (927) were current smokers and 39% (593) were former smokers. After five annual CT examinations, 3,356 uncalcified lung

nodules were identified in 1,118 (74%) individuals with 2% of these (68/3356) identified as primary lung cancers (Table 1). The authors concluded that CT screening allows for the early detection of nodules, with a high rate of benign nodules detected (Swensen et al 2005).

Table 2 Five Year Results of CT Lung Screening

Uncalcified Nodules	74% of individuals
Nodules <4mm	61%
Nodules 4-7 mm	31%
Nodules 8-20 mm	8%
Nodules >20 mm	<1%
False Positive Nodules	96%
Lung Cancers	68 in 66 individuals (4%)
Lung Cancers First Exam	31 (3%)
Subsequent Lung Cancers on Annual CT	34 (3%)
Interval Cancers	3
Deaths from lung cancer	9
Stage I disease and CIS	47.7%
Stage II disease	20%
Stage IIIa disease	16.9%
Stage IIIb and IV disease	15.4%

Currently, several large observational and randomised trials are ongoing or planned (see Other Issues). Recently, Milleron et al 2004 reported preliminary results of a randomised screening trial (level II screening evidence) of CT versus chest X-ray which plans to enrol 40,000 asymptomatic individuals[23]. Individuals were randomised to either CT (n=180) or X-ray (n=173). CT detected 89/180 (49.5%) non-calcified nodules and of these, six patients were diagnosed with lung cancer. Chest X-ray revealed 12/173 (7%) of individuals with non-calcified nodules, one of whom was diagnosed with lung cancer (Milleron et al 2004).

In a recent pilot study (level II screening evidence) a total of 1,660 individuals were randomised to CT screening and 1,658 to chest X-ray (Gohagan et al 2005). Demographics and smoking history were similar across the two arms[24]. A total of 40 and 20 lung cancers were detected in the CT screen and chest X-ray groups, respectively. In the CT screen group, 48 per cent of cases were Stage I cancers and 16 per cent were Stage III—IV cancers. In the chest X-ray group 40 and nine per cent of cases were Stage I and Stage III—IV cancers, respectively.

[23] Aged 50–75 years, current or former smokers (more than 15 cigarettes/day during a minimum of 20 years).
[24] A total of 59% were male, 68% were age 55—64 years (32%; age 65—74 years), and 58% were current (42% former) smokers; the median pack years of smoking was 54.

Table 2 Total lung cancer cases by arm, stage and method of detection

Screen detected	CT Screen Stage						*Chest X-Ray Stage*					
	I	II	III	IV	Unk	Total	I	II	III	IV	Unk	Total
Baseline	16	3	6	3	2	30	6				1	7
Year1	2		5	1		8	2	1	4	1	1	9
Interval	1			1		2						4
Total (%)	19 (48)	3 (8)	11 (28)	5 (13)	2 (5)	40 (100)	8 (40)	1 (5)	5 (25)	4 (20)	2 (10)	20 (100)

Unk = unknown

There are few published papers which report on the ability of CT screening for lung cancer to reduce mortality. Several CT screening trials reporting on mortality are ongoing, however the assessment of this outcome requires a long follow-up period.

A recently published large scale study (n=31,567 asymptomatic persons) reported on 10-year follow-up outcomes of patients with Stage I lung cancer detected with CT screening (level IV screening evidence) (Henschke et al 2006). Diagnosis was confirmed by biopsy. CT screening resulted in a diagnosis of lung cancer in 484 asymptomatic participants. Of these, 412/484 (85%) had clinical Stage I lung cancer, and the estimated 10-year survival rate was 88 per cent in this subgroup (95% CI 84-91) regardless of type of treatment received. Surgical resection was performed in 375/412 (91%) of these patients, however only 302 underwent resection *within one month of diagnosis.* The 10-year survival rate in this sub-group was 92% (95% CI 88-95). Eight participants with clinical Stage I cancer did not receive treatment and died within five years after diagnosis (Henschke et al 2006).

An earlier Japanese study reported a reduction in mortality for patients with lung cancers detected by CT screening (level III-2 screening evidence). CT scanning was performed on 15,342 people. Of the lung cancers detected, 78 % were Stage I, with a mean diameter of 1.5 cm, and only 14 percent were either Stage III or IV. The overall five-year survival rate improved, from 49 per cent for cases detected by chest radiography to 84 percent for those detected by CT [25](Kakinuma 2003).

There were no studies available which directly compared screening for lung cancer with CT to X-ray.

2007 COST IMPACT

Preliminary cost-effectiveness studies report large variations in the estimated cost impact of CT screening for lung cancer. This may be due in part to differences in estimating the efficacy of screening and the use of different lung cancer risk groups. One study used a computer-simulated modelling analysis of a hypothetical cohort of 100,000 current, quitting and former heavy smokers. This model assumed that few

[25] The total number of cancer cases detected was not available.

late stage cancers would be detected. Incremental cost-effectiveness was estimated to be US$116,300 per quality-adjusted life-year gained (Mahadevia et al 2003). A study by Wisnivesky et al (2003) used cost data from the I-ELCAP study screening study and estimated incremental cost-effectiveness to be US$2500 per person-year of life saved.

An Australian study compared the cost impact of annual CT screening and treatment for 5-years to no screening and treatment in symptomatic 60-year old patients in a cohort of 10,000 individuals (Manser et al 2005). A Markov model was used to examine the relationship between efficacy in terms of the expected reduction in lung cancer mortality at seven years (assuming a reduction by 27% in mortality)and cost effectiveness. A value of $50,000 per life-year saved is used to define cost-effectiveness. The authors report that CT screening for lung cancer patients would be cost-effective if screening very high-risk population groups results in mortality reduction of more than 20% or the cost of CT screening falls substantially.

2007 Ethical, Cultural or Religious Considerations

Recent studies indicate that 25-60% of screening CT scans of smokers and former smokers will show abnormalities and that most of these abnormalities are not lung cancer. However, these abnormalities such as scars from smoking, areas of inflammation, or other non-cancerous conditions may mimic lung cancer on scans and may require additional testing. These tests may cause anxiety for the participant or may lead to unnecessary biopsy or surgery.

2007 Other Issues

In the United States, the National Lung Screening Trial, sponsored by the National Cancer Institute is currently in progress (U.S. National Cancer Institute 2006). This study aims to compare the ability of CT and standard chest X-ray to detect lung cancer and will examine which modality is more effective at reducing mortality in approximately 50,000 current or former smokers (level II screening evidence). Follow-up will continue to 2009. Another randomised trial is planned for the United Kingdom.

Although the available studies seem to suggest that CT screening is a promising tool for lung cancer detection, it is important to consider biases inherent to uncontrolled studies. Generally randomised trials are considered the gold standard for demonstrating a reduction in mortality. Lower level evidence study design cannot establish the effectiveness of screening tools in improving survival because of screening biases such as length-time, lead-time and overdiagnosis bias (Manser et al 2004 and Rossi et al 2005). However, these studies may provide an important evaluation of new screening techniques by providing data on test accuracy, feasibility and acceptability.

2007 CONCLUSION:

The main outcome for a successful screening program is for decreased morbidity and mortality from the targeted disease. It appears that lung cancer screening is effective in detecting early stages of the disease. However, to date, there is insufficient evidence to suggest that CT screening reduces mortality although it is clear that tumours are detected at an earlier stage compared to chest X-ray and standard clinical practice. Most of the evidence available at the time of preparing this summary comes from uncontrolled studies.

2007 HEALTHPACT ACTION:

Given that a large randomised controlled study is in progress, a clearer picture of whether CT screening can reduce morbidity in a high risk patient group may be ascertained. It would be prudent to await the results of this and further trials, therefore HealthPACT recommended that this technology be monitored in 12 months time.

2007 SOURCES OF FURTHER INFORMATION:

Gohagan, J. K., Marcus, P. M. et al (2005). 'Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer', Lung Cancer, 47 (1), 9-15.

Henschke, C. I., Yankelevitz, D. F. et al (2006). 'Survival of patients with stage I lung cancer detected on CT screening', N Engl J Med, 355 (17), 1763-1771.

Kakinuma R. (2003). 'Low-dose helical CT screening for lung cancer: the Japanese experience and perspective. In: Proceedings of the International Association for the Study of Lung Cancer Workshop, Tokyo, November 7, 2003:18. abstract.

Mahadevia, P. J., Fleisher, L. A. et al (2003). 'Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis', Jama, 289 (3), 313-322

Manser, R., Dalton, A. et al (2005). 'Cost-effectiveness analysis of screening for lung cancer with low dose spiral CT (computed tomography) in the Australian setting', Lung Cancer, 48 (2), 171-185.

Manser, R. L., Irving, L. B. et al (2004). 'Screening for lung cancer', Cochrane Database Syst Rev, (1), CD001991.

Milleron B. (2004). 'Screening for lung cancer: feasibility study of a randomized trial comparing low dose spiral CT and chest X-ray. J Clin Oncol 2004;22(Suppl.):661s [abstract 7183]

Mulshine, J. L. & Sullivan, D. C. (2005). 'Clinical practice. Lung cancer screening', N Engl J Med, 352 (26), 2714-2720

National Cancer Institute of Health (2006). National Lung Screening Trial. What is NLST? [Internet]. National Cancer Institute of Health. U.S. National Institutes of Health. Available from: http://www.cancer.gov/nlst/what-is-nlst [Accessed 19th December 2006].

NCCI Working Group on Lung Cancer Screening (2003). Lung cancer screening by helical computed tomography. [Internet].National Cancer Control Initiative, Melbourne. Available from: www.ncci.org.au [Accessed 20th December 2006].

Read, C., Janes, S. et al (2006). 'Early Lung Cancer: screening and detection', Prim Care Respir J, 15 (6), 332-336.

Rossi, A., Maione, P. et al (2005). 'Screening for lung cancer: New horizons?' Crit Rev Oncol Hematol, 56 (3), 311-320.

Swensen, S. J., Jett, J. R. et al (2005). 'CT screening for lung cancer: five-year prospective experience', Radiology, 235 (1), 259-265.

The Cancer Council Australia (2004). Assessment and Management of Lung Cancer. Evidence based guidelines. A Guide for General Practitioners. [Internet].Available from: http://www.cancer.org.au/documents/lungcancerGPcard.pdf [Accessed 21st December 2006].

Unger, M. (2006). 'A pause, progress, and reassessment in lung cancer screening', N Engl J Med, 355 (17), 1822-1824.

Wisnivesky, J. P., Mushlin, A. I. et al (2003). 'The cost-effectiveness of low-dose CT screening for lung cancer: preliminary results of baseline screening', Chest, 124 (2), 614-621.

LIST OF STUDIES INCLUDED

Total number of studies	
Level II screening evidence	2
Level III-2 screening evidence	1
Level IV screening evidence	3

SEARCH CRITERIA TO BE USED:

Lung/radiography
Lung Neoplasms/mortality/ radiography
The lung screening study research group
Tomography, X-Ray Computed