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Screening for lung cancer utilising computed tomography

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PRIORITISING SUMMARY

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.

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.

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).

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.

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).

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 1 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[1]. 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[2]. 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.

[1] Aged 50–75 years, current or former smokers (more than 15 cigarettes/day during a minimum of 20 years).
[2] 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 [3](Kakinuma 2003).

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

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

[3] 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.

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.

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 over-diagnosis 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.

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.

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.

SOURCES OF FURTHER INFORMATION:

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

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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