HELICAL CT SCREENING FOR LUNG CANCER — FUTURE DIRECTIONS

Summary of the workshop sponsored by the National Cancer Control Initiative

22 May 2001
Melbourne, Victoria
The Workshop

‘Helical CT Screening for Lung Cancer – Future Directions’ the workshop sponsored by the National Cancer Control Initiative (NCCI) was held on 22 May 2001 from 2pm to 6pm at the Cancer Control Research Institute, 100 Drummond Street, Carlton, Victoria.

Objective

The objective of the workshop was to discuss helical CT scanning as a screening technique for lung cancer and its future directions in Australia.

Origin

The workshop arose from suggestions to the NCCI that helical CT screening for lung cancer was an important topic and that there were a number of individuals and centres in Australia who were interested in pursuing activities in this area. A workshop might therefore be useful to provide an overview of the current position of helical CT screening for lung cancer and to assist in reaching consensus on what are the key issues that could be addressed in Australia. Such a workshop might also lead to collaboration between different centres that could be beneficial.

Structure

The workshop was Chaired by Professor Richard Smallwood AO, Commonwealth Chief Medical Officer and Professor Mark Elwood, Director of the NCCI. The workshop was open to all interested people and there was no cost to attendees.

The workshop comprised seven presentations and an audience discussion. Each presentation was followed by a short period of open discussion. A longer audience discussion took place after the presentations, to explore the issues surrounding helical CT scanning as a screening technique for lung cancer and discuss the way forward for Australia. Professor Smallwood Chaired the presentation section of the workshop and Professor Elwood Chaired the audience discussion.

Attendance

Approximately 60 people attended the workshop. The audience was comprised of thoracic physicians, radiologists, oncologists, thoracic surgeons, epidemiologists, Commonwealth and State health officials, scientists, radiology staff and project officers.

Workshop Summary

This document contains a summary of the workshop proceedings. For each presentation there is a short overview, a presentation abstract (as provided by the speaker) and a summary of the discussion that followed. A summary of the audience discussion held after the presentations is also included.
Screening for Lung Cancer with Helical CT: Current and Planned Studies.

Renee L. Manser, Clinical Epidemiology Unit, Royal Melbourne Hospital, Parkville, Victoria, 3050

Overview
The presentation covered the current and planned international studies that are aiming to evaluate helical CT scanning as a screening technique for lung cancer. The international studies discussed were the National Cancer Institute (NCI) pilot trial (current), United Kingdom (UK) pilot study (planned), European study (planned), American College of Radiology Imaging Network study (planned) and the Mayo Clinic study (planned). Information was also presented on the Prostate, Lung, Colon and Ovarian (PLCO) cancer screening trial, which is underway in the United States (US) and is using chest X-ray rather than helical CT scanning to screen for lung cancer.

Abstract
Previous randomised controlled studies have not demonstrated a benefit from lung cancer screening with regular chest radiography. However, none of these studies included a control group that did not receive some type of screening. The PLCO (Prostate, Lung, Colon and Ovarian) cancer screening study is currently being conducted in the USA. In this large study, male and female participants who are randomised to the intervention group will be offered an annual chest X-ray for 3 years. The control group will not be offered active screening. Participants in the intervention group are also offered screening tests for colon, ovarian (females) and prostate (males) cancer. The primary outcome is disease specific mortality. The results are expected in 2015. Recent uncontrolled studies have shown that helical CT is a more sensitive tool for detecting early lung cancer compared with plain chest radiography. Several large randomised controlled studies are now being planned to evaluate whether screening with CT can reduce mortality from lung cancer. A pilot study is currently being conducted in the USA. This study has enrolled a total of 3000 participants (smokers and ex-smokers, aged 55-74). The intervention group was offered a helical CT (baseline and 12 months) and the control group was offered chest radiography. The study has been designed to examine the feasibility of conducting a larger trial. The outcomes being considered include acceptability to participants and compliance with screening. Recruitment is complete and follow-up is ongoing. A pilot study is also being planned in the United Kingdom. This study will recruit 2000 participants (current smokers, aged 60-75). The intervention group will be offered screening with helical CT at baseline and 12 months and the control group will not be offered active screening. Blood samples will be collected for biomarkers. The full study is expected to require at least 40,000 participants. Funding is currently being sought for this study. A multi-centre European study is also being planned in which the control group will be offered regular chest radiography and the intervention group will be offered helical CT. The American College of Radiology Imaging Network is also planning a multi-centre study that will recruit high-risk participants. The intervention group will be offered helical CT and the control group will be offered usual care. This study is still in the planning stages.
Discussion

Issues discussed were as follows:

- **Collaboration, either current or planned, between the international groups, including any preplanned meta-analyses or shared biomarkers**

Mention was made that the UK group is actively collaborating with the European group and that it is possible that they may seek wider collaboration. Information about the NCI pilot trial is available from the Internet website of the NCI ([http://www.nci.nih.gov](http://www.nci.nih.gov)) and comment was made that recruitment for the pilot trial is now complete.

Information on helical CT screening for lung cancer is also available from the Cornell University Internet website ([http://www.med.cornell.edu](http://www.med.cornell.edu)). It was mentioned that this included information from presentations given at international workshops on lung cancer screening and information relating to collaboration using intermediate markers. Little specific information appears to be available as to which biomarkers are being examined. It is thought that different groups may be collecting different biomarkers at this stage.

- **Importance of study design around possible collaboration and sharing of data**

There was comment that consideration should be given to the importance of study design around potential collaboration and sharing of data. The example was given of the experience of screening trials for colorectal cancer in the UK and Europe, where each study was under-powered but by being able to pool the study results an important contribution was made. Dr Manser commented that the UK group is interested in collaborating from that point of view with other international groups.

- **Usefulness of lung cancer specific mortality as an end point**

The usefulness of lung cancer specific mortality as an end-point was questioned. It was pointed out that while lung cancer specific mortality maybe a useful end point for efficacy, it may be less so for effectiveness, as smokers are at risk from other causes for mortality. Overall mortality and survival may be much more pragmatic end points.

In reply, it was highlighted that while all cause mortality is of interest most studies would have insufficient power to examine this. Survival was not thought to be an adequate outcome in screening studies due to the bias associated with screening (over-diagnosis bias, lead-time bias, etc).

- **Funding status of international studies and whether international organisations are potential funding sources for Australian investigators**

Discussion was held regarding the funding status of the international studies and whether the organisations sponsoring these studies might be potential funding sources for Australian investigators. It was thought that it was likely that the proposed international studies would be funded. The UK proposal is in the process of being reviewed and is through to the second round of its funding process. For the studies in the USA, it was thought that the NCI would fund a study although which one and in what form was unknown. In relation to Australian investigators obtaining funds from the international organisations, it was felt that it was very unlikely that they would fund a study here.
• Screening interval

The issue of the screening interval in the international studies was raised and the question asked as to whether in the design of these studies there has been any discussion as to the optimal timing for screening procedures. The point was made that helical CT scans are likely to detect small pulmonary nodules and that one strategy for dealing with small nodules is to wait and see whether they are growing. The interval between scans is therefore an important issue. If left long enough a nodule may metastasise or the biology become predetermined.

Dr Manser commented that little information on the optimal interval for screening is available at this stage. Most studies are looking at performing an annual screen. It was pointed out that screening too frequently increases the risk of false-positive results. The period of observation currently being considered was felt to be appropriate for the moment, although it was acknowledged that it is not based on firm data.

There was a comment that the American College of Respiratory Physicians had issued a joint statement in which, for indeterminate nodules, six-monthly follow-up scans were recommended. It was further commented that some international studies are planning three-monthly follow-up scans for indeterminate nodules.

• Recruitment strategies

The question was asked as to how the international studies are recruiting, or are planning to recruit, screeners and whether there are any lessons for the Australian proposals. It was mentioned that the UK group is planning to recruit through general practice, while in the USA it was thought that much of the recruitment would be conducted through advertising and direct mail-outs.

It was commented that recruiting patients is a big undertaking and that with the PLCO trial, for the pilot study alone some 166 000 flyers were distributed to recruit 500 patients per centre for each of six centres.

• Target age groups

There was discussion as to the age of the screeners in the international studies. Mention was made that there are varying minimum ages in these studies for the people being screened. In addition, there is a question as to what should be the maximum age of those being screened, as in older age groups the issue of competing causes of mortality arises.

Most of the international studies are looking at an upper age limit of 74-75 years. It was felt that this is a reasonable limit given the competing causes of mortality in this age group. There has been some suggestion that screening may be more effective in the older population.

• Helical CT technology

The issue of which generation technology of helical CT scanners the international studies are using (newer generation multi-slice CT scanners or the older CT scanners) was raised, as there are detection issues with the different scanners. It appears that all the international studies are planning to use to newer generation CT scanners. Furthermore, the UK group is attempting to secure funding for mobile CT scanners that are specifically designed just for screening.
Aetiology of Small Peripheral Opacities in an At-risk Population

David C. Cameron, Department of Diagnostic and Interventional Radiology, Royal Perth Hospital, Perth, WA, 6847.

Overview
The presentation described plans for a novel pilot study in Western Australia (WA) that aims to evaluate a management strategy for pulmonary nodules detected by helical CT scans and which could provide local information on lung nodules. In this study, it is proposed to offer patients who have had a lesion detected by a helical CT scan an ‘immediate’ removal of the lesion, that is removal of the lesion as soon as logistically possible after the screening scan. A design for a hook wire that has been developed in WA and which is considered to offer improved displacement rates was described and demonstrated.

Abstract
Considerable energy is being generated in the search for a screening test for lung cancer. Low dose helical computed tomography (CT) has the ability to detect small nodules and the early prevalence screening data has been encouraging, in so far that there are multi-centre trials under way in a number of countries. Survival from the time of diagnosis will be reported, however, these are subject to various “biases” (lead time, length time and over diagnosis).

The cost of these trials is huge and the numbers needed are large. Questions that need to be asked are:

- Is size related to biological behaviour?
- Does it really matter whether it is 5mm or 10mm?
- Does size influence mortality in the long run?
- Will the search for benign lesions prove too costly in areas where there is a high instance of granulomata?

We have decided that helical CT is likely to produce the ‘lesions’, but we would like to reduce the numbers and cost and assess this problem as a Management Strategy – that is, will VAT tell us what our lump lesions are in our area? Will it be the best Management Strategy and will it change clinical practice in our area?

This presentation will lay down the trial design, the role for hook wire localisation and the costs entailed.
Discussion

Issues discussed were as follows:

- **Patients with multiple nodules**

  The question was asked as to what would be done in the proposed study for patients with multiple nodules. In reply, Dr Cameron gave his personal opinion. He felt that many patients would have multiple lesions and that there would be a need to specify lesion morphology, with round and spiculated lesions being considered as cancers until proven otherwise and linear lesions or scars being followed with a conservative approach. Patients who did not wish to have the lesion removed immediately will be followed with a conservative approach and patients entitled to thoracotomy could undergo this procedure if they wished. For patients with multiple nodules, Dr Cameron indicated that at present he did not have an answer, however, it was his opinion that such patients would be followed with a conservative approach.

- **Size and depth of the nodules to be removed**

  In discussion as to the minimum size of the nodules to be removed, it was indicated that the proposal was to remove lump lesions as small as 5 mm as the tools to do so are available. Subsequent comments were made as to whether it was necessary to remove such small lesions, as the benefits of removing them may be outweighed by the risks of surgery.

  The point was also raised that many nodules are not peripherally based and are not accessible by either wedge resection or the technique discussed in the proposed study. The question was asked as to what would be done for these deeper nodules. In reply, it was discussed that the proposed protocol was for nodules that are 3 cm from the surface (pleura) and nodules that are deeper than this have to be treated with a conservative approach.

  A comment was made from the audience that there is a technique being developed in Melbourne which allows deeper lesions to be accessed with minimal invasion. This was for general information.

- **Patient information as to the risks associated with the procedure**

  There was discussion as to what information patients need to be given regarding the risks associated with the proposed procedure, as for some patients the procedure may be performed to remove entirely benign lesions. This issue was addressed by a thoracic surgeon in the audience who indicated that patients would need to be fully informed of all the risks associated with the operation, namely bleeding, infections, air leakage, deep vein thrombosis, myocardial infarction, pulmonary embolism and ARDS (acute respiratory distress syndrome).

- **Timing of the biopsy procedure for indeterminate nodules**

  Clarification was sought as to the definition of ‘day-one’ with reference to performing the biopsy procedure for indeterminate nodules. The point was made that indeterminate nodules can be inflammatory and it was asked whether time was allowed in the proposed study for indeterminate nodules to settle prior to biopsy.

  ‘Day-one’ was clarified as being ‘as soon as possible’ logistically after the screening scan. In the discussion that followed it was indicated that the protocol for such lesions would still be to perform a biopsy as soon as logistically possible after the screening scan, as otherwise the patient would have to be followed up to 24 months before discharge.
• Patient characteristics and recruitment

Discussion was held regarding which patients would be eligible to participate in the study and how it was planned to recruit these patients. It was indicated that the patients would all be smokers and have to meet inclusion and exclusion criteria. Patients would undergo a Helical CT screening procedure that was approved by an Ethics Committee. Recruitment was planned via advertising.
Proposed Lung Cancer Screening in Central Sydney – Planning Issues

Michael J. Millward, Sydney Cancer Centre, Royal Prince Alfred Hospital, Camperdown, NSW, 2050.

Overview
The presentation described a proposed study for lung cancer screening in Central Sydney. The goals of a lung cancer screening program were discussed together with possible options for Australia to pursue in this area. An outline of what was thought to be a feasible project involving screening 500 subjects recruited over two years was presented. Information was given on the evaluations to be undertaken and the clinical follow-up required. A detailed algorithm for the identification of target subjects and their management was described together with information on a preliminary budget.

Abstract
The recent advances in low-dose spiral CT scanning have made the issue of lung cancer screening come again to the forefront. Older screening trials have failed to prove beneficial primarily because of the failure to understand the difference between surgically resectable and curable NSCLC. Chest X-ray does not have the resolution to diagnose early (1 cm) disease where resection is highly likely to be curative. In Chest X-ray trials, only about 50% of the lesions detected by screening were stage I disease, compared to almost 90% in low dose spiral CT trials. Advances in molecular genetics, particularly the detection of aberrant DNA methylation patterns, have the potential to detect very early malignancy in sputum or blood, but cure will require anatomical localisation until more potent differentiating or chemoprevention agents become available.

In Central Sydney, oncologists, respiratory physicians, radiologists, laboratory scientists and health outcome researchers have all shown interest in developing and evaluating a lung cancer screening protocol. An algorithm for the identification of subjects and their management should radiological abnormalities be detected is being prepared. Planned ancillary projects include the collection of blood (and any biopsy material) for DNA methylation analysis, and a detailed community-based survey of attitudes, trade-offs, and willingness to participate in screening. A crucial part of the analysis of any screening for lung cancer will be the rate of smoking cessation in screen participants.

Major problems include the need to identify funding to cover the costs of screening scans, and the complex co-ordination of subject enrolment and dissemination of results to subjects and GPs. As only a small number of cancers are likely to be picked up in an initial prevalence screen, provision for long-term follow-up needs to be made (and costed). To screen 500-1000 high-risk subjects will require funding that will challenge traditional sources of research support. The desirability of value-adding both basic science and public health research is also a challenge to identify the most appropriate funding sources.
**Discussion**

Points discussed were as follows:

- **Potential medicolegal consequences**

  The question was asked as to whether information obtained during the screening study would be sequestered away from future medico-legal consequences. Dr Millward commented that while he could not answer the question from a legal point of view, the study would obviously be a research activity and that patient consent would be required. It was discussed that as part of the consent for any screening procedure, the patient has to be informed that there are false positive and false negative rates (although these rates are currently not known and would be one finding from the study). Patients have to be informed that undergoing screening does not guarantee that they will not develop lung cancer in the future.

- **Increased detection of small cancers**

  A comment was made that while helical CT scanning will detect small peripheral adenocarcinomas, the technology is less able to detect small central cancers and that sputum cytology may be an important tool in this regard. It was further commented that it is important to know with the multi-detector CT scanners, whether 5 mm or 10 mm collimations would be used as this affects the detection of small nodules. It was suggested that if possible the 5 mm type is preferable.

- **Medicare coverage of associated costs**

  The issue of whether Medicare would cover items containing screening in the description was raised and it was thought that this is doubtful. There was discussion as to whether once a lung lesion has been found on a screening program that requires diagnosis, biopsy, follow-up etc, whether this represents legitimate treatment of a condition rather than screening and as such could be covered by Medicare. It was agreed that Medicare would not cover the costs of the actual screening procedures.

- **Screening interval**

  In the proposed study, it was planned to perform an annual helical CT scan in an at-risk group. The comment was made that as tumours can develop in a six-month period, whether a different screening interval should be considered. In reply, Dr Millward commented that while it would be ideal to enrol 1000 patients in a study where they could undergo a prevalence screen and the negative or equivocal subjects be followed-up with further regular screening, the costs involved in performing the screening would rise dramatically. It was felt that it was not realistic to propose such a study, as this had implications for its funding potential.
Proposal for an Australian Pilot Study of Low Dose Helical CT Scan Screening for Lung Cancer.

Renee L. Manser¹, D. Ball², L.B. Irving³, J. Vincent⁴, G. Byrnes¹, E. Lau² T. Sasse⁵, D.A. Campbell¹.

Overview
The presentation outlined a proposal for a pilot study that could be conducted in order to assess the feasibility of undertaking a large randomised controlled trial in Australia. Details of the proposed aims, target group, recruitment and inclusion and exclusion criteria were presented. An algorithm for evaluating the results of helical CT scans was outlined along with the potential study outcomes. Issues of incorporating smoking cessation elements and potential collaboration were discussed and issues that may impact on feasibility highlighted.

Abstract
Low dose helical computed tomography (CT) has recently been used to screen for occult lung cancer in high risk individuals in order to detect lung cancer at a stage when it is amenable to potentially curative resection. The results of uncontrolled studies conducted overseas are promising but there is currently no data from the Australian population.

We propose a small randomised controlled pilot study. We plan to recruit 1000 asymptomatic individuals at high risk of developing lung cancer from the community. Five hundred individuals will be randomised to undergo screening with helical CT at baseline and 12 months later and 500 individuals will not be offered any screening during the study period. Once screening has ceased, follow-up will be for a further 1 year in both groups. This study will provide data on the feasibility of conducting a large Australian randomised controlled study evaluating the effectiveness of screening with low-dose helical CT at reducing lung cancer mortality. We will also evaluate the accuracy of screening and diagnostic algorithms, developed in North America, when applied to the Australian population.

We plan to evaluate the costs and harms associated with screening from the Australian perspective and perform a preliminary cost-effectiveness analysis based on projected estimates of effectiveness. The study will also examine the effect of screening on subsequent smoking behaviour and smokers in both the intervention and control groups will be offered counselling services for smoking cessation. We have adopted a similar methodology to a study currently being planned in the United Kingdom so that a pooled data analysis might be possible in the long term.

(1) Clinical Epidemiology Unit, Royal Melbourne Hospital, Parkville, Victoria, 3050
(2) Peter MacCallum Cancer Institute, East Melbourne, Victoria, 3002
(3) Department of Respiratory Medicine, Austin & Repatriation Medical Centre, Heidelberg, Victoria, 3084
(4) Radiology Department, Royal Melbourne Hospital, Parkville, Victoria, 3050
(5) Latrobe Valley Hospital, Traralgon, Victoria, 3844


Discussion

Issues discussed were as follows:

- **Diagnosis of scan-detected nodules**

Discussion was held around the issue of how pulmonary lesions detected by helical CT scans would be diagnosed and classified. The point was raised that confirmation of biopsy results is an important issue and that the logistics of diagnosis and assessment of scan-detected nodules needs to be considered in any screening study. Dr Manser commented that the approach to diagnosis and classification could be subject to local procedures and availability. In their proposed study, they would consider replicating the ELCAP (Early Lung Cancer Action Project) study in which a lot of fine needle aspirates were performed, as this is both well documented in the literature and was associated with low complication rates.

The suggestion was made that a negative, non-malignant fine needle biopsy result on a very small nodule is a finding that should be considered with caution and the point re-iterated that the rate of benign nodules in Australia is at present unknown. The question was asked as to whether performing core biopsies of small lung nodules had been considered. There was mention from the audience that one hospital in Melbourne does perform core biopsies of larger lung lesions with similar complication rates to fine needle aspiration.

A question was raised as to whether Hounsfield Unit Density associated with contrast might be a useful discriminator for benign nodules. Dr Manser indicated that she was aware of a study from the US suggesting that this is useful discriminator for benign nodules, but is unaware that the study has been validated or replicated and also how widely this is used.

- **Potential for screening asbestos-exposed subjects**

The issue of risk factors for lung cancer was raised along with the potential for exploring screening in subjects at very high risk for lung cancer, namely subjects who are smokers and have been exposed to asbestos. It was mentioned that in the ELCAP study, 14% of participants had asbestos exposure and that there is interest in a sub-group analysis from this study. It was questioned whether such a sub-group analysis has implications for any Australian investigation.

At present there is considerable interest in screening in asbestos exposed workers. The point was made that it cannot be assumed that results from a population screening study can be generalised to an asbestos exposed group and that it may be worth looking at the asbestos exposed group in a separate study.

- **Inclusion of subjects treated for head and neck carcinomas or with primary lung cancer in proposed Australian screening studies**

A question was asked about the inclusion in the proposed Australian screening studies of patients previously treated with curative intent for head and neck carcinomas or patients with primary lung cancers. These are groups known to be at great risk for the development of new primary lung cancer and might represent a potential area of interest.

In addressing the question, Dr Manser pointed out that when planning a population-based study it can be difficult to include very specific high-risk groups as this could lead to imbalances in the study design. A separate study for that group might be useful due to the problem of potential cancer recurrence.
Dr Millward commented that they had looked at this issue and that these subjects are not really a population group. The prevalence of lung cancer in this group is around five percent, which is less than double the ELCAP prevalence rate. Significant numbers of people would therefore still need to be screened in order to detect cancers. It was acknowledged that the ratio of malignant nodules to non-malignant nodules may be slightly more favourable, however, it was felt that this group could be studied as a sub-group in a different study.

- **Comment on what should Australia be doing**

Comment was called for on what should Australia be doing in relation to helical CT screening for lung cancer. In reply, Dr Manser gave her opinion that she hoped that some sort of collaboration and consensus would come from the meeting as to how Australia can best inform the debate and place itself in a position to inform policy when the results from the international studies are known. There is a need for more information relating to cost-effectiveness in the Australian population and information about lung cancer epidemiology. There is the need to identify the target group, including their suitability to undergo screening, and also the acceptability of screening to these people.
Value Adding to Helical CT Screening

Kwun M. Fong, Department of Thoracic Medicine, The Prince Charles Hospital, Rode Road, Chermside, QLD, 4032.

Overview
The presentation described a variety of techniques that could value-add to a screening study for lung cancer utilising helical CT scanning. Techniques discussed included molecular risk assessment (polymorphisms of DNA repair genes, glutathione-S-transferase gene system, Cyp1A1 gene), computerised radiology (energy subtraction digital chest X-rays, computer-aided detection), non-imaging detection (biomarkers – heterogeneous nuclear ribonucleoprotein A2/B1, promoter methylation) and other interventions such as smoking cessation. In addition, fluorescent bronchoscopy, a high frequency chest wall oscillator for expectorating sputum in individuals who do not usually cough and the Queensland Integrated Lung Cancer Outcomes project were mentioned.

Abstract
There has long been interest in screening to detect lung cancers when they are smaller and presumably at an earlier and more curable stage. Most recently, a powerful, new screening tool has become available in the form of helical low dose CT scanning. A considerable amount of research is now investigating its potential role in combating lung cancer.

Paralleling the technological developments in imaging is the increasing knowledge of the pathogenesis and biology of lung cancer, leading to novel methods for lung cancer screening and early diagnosis.

This presentation will discuss the possible complementary value of:

- Molecular epidemiology in defining populations at highest risk of developing lung cancer, as only a proportion of heavy smokers develop lung cancer
- Refined chest radiographic imaging, such as energy subtraction digital CXRs, to improve the sensitivity for lung nodule detection.
- Novel sputum and blood biomarkers for detecting lung cancer cells
- Primary prevention smoking cessation opportunities through screening programs

Large-scale screening programs are likely to be costly, and should be cost-effective. We believe that any planned studies in Australia, could value-add to their potential significance, by considering the additional testing of complementary techniques. These could be achieved with relative ease and modest cost, by planning their incorporation at an early stage based on the proposed infrastructure.
Discussion

Issues discussed were as follows:

- **Molecular marker assessment – cost in relation to helical CT scans**

  The question was asked as to what is the estimated cost of assessing for the presence of molecular markers using the newly available technology, relative to the cost of a helical CT scan. Dr Fong indicated that it depended on the type of technology being used. For example, with TacMan technology the estimated cost is two dollars per assay per sample, while for the Micro-array technology (which is very recent) it was thought in Queensland would cost two hundred dollars per slide. It was pointed out, however, that a Micro-array is capable of looking at up to 40,000 genes at one time.

  It was discussed that, while this is potentially expensive technology, it is still relatively recent and as use of the technology increases it is likely that the costs will come down, as happened previously with automated DNA sequencing.

- **Specificity of methylated DNA for indicating the presence of malignancy**

  The issue of how specific circulating methylated DNA is for indicating the presence of a malignancy within the body was raised. At present this is unknown. Methylation was only described around 18 months to two years ago and studies are currently being conducted to address this question. It is potentially very important. It is known that free DNA exists in plasma and that additional DNA is released when a tumour is present. This represents a potential target that could be exploited to detect cancer, however, much remains to be determined.

  The comment was made that a six-monthly blood test for heavy smokers or former heavy smokers that could screen for the presence of malignancy represents a goal.

- **Which molecular markers should be assessed in sputum**

  The question was asked as to which molecular markers should currently be assessed in sputum, given the current state of knowledge. In reply Dr Fong indicated, that for sputum conventional cytology should be performed as it provides a standard to assess against, however, heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNP A2/B1) is a very promising molecular marker. This marker is detected using immunohistochemistry, which makes it easier to assess and a tool that is applicable to many centres.

- **Potential identification of malignant nodules without the need for invasive tests**

  Discussion was held around the topic of whether the point will come at which the key molecular markers and biomarkers have been determined and malignant lung nodules can be identified without the need for invasive testing. It was mentioned that it is uncertain as to whether this point will ever be reached. It is hoped that technology will allow for the identification of people at highest risk and that tools can be developed to assist with early diagnosis and prognosis.
Management of Scan-detected Nodules


Overview
The presentation outlined a strategy for the evaluation and management of screen-detected pulmonary nodules. The presentation addressed the issue of the solitary pulmonary nodule (SPN) and described a management algorithm that aimed to provide a balanced approach. Information was presented on the types of SPN encountered, the growth rates of malignant SPN and the relationship of doubling time to malignancy. In the management algorithm, nodule calcification patterns, stability and size were incorporated along with biopsy, staging and treatment. There was discussion of the wait and watch approach and quantitative decision approaches involving calculating the probability of malignancy using Bayes theorem.1

Abstract
With population based screening, it is expected that a wide variety of asymptomatic pulmonary abnormalities would be detected. As the reason for screening is to detect early lung cancer, a rational plan has to be in place to evaluate the shadows that are found. It is not known what the likelihood ratio for benign or malignant disease is across Australian cities, but screening should clarify this.

It is known that advanced disease can be quite asymptomatic. If detected, these patients would undergo routine procedures for evaluation, such as fine needle biopsy or bronchoscopy biopsy, for staging and management.

The problem is how to evaluate the small nodule of under 3 cm in diameter – observe with X-ray follow-up, VATS biopsy with guidewire placement preoperatively, PET scanning etc. These tests rely on the specialist expertise being available in the centres were screening is taking place.

This presentation will discuss the options available (and suggest a plan) for evaluating and managing patients in whom pulmonary nodules are detected.

Reference:
Discussion

Issues discussed were as follows:

- Lesion size in relation to the management algorithm

Comment was made that this presentation summarised one of the major problems and that is what to do with the screen-detected nodule. There was, however, some difference of opinion expressed relating to nodule size as presented in the management algorithm.

It was indicated that it is not desirable to be detecting pulmonary lesions 3 cm in diameter and the problem is what to do with lesions that are less than 5 mm or in the 5-10 mm range. It was pointed out that as nodules decrease in size it becomes increasingly difficult to see their margins and calculate the percentage of calcification based on partial volume averaging. In addition, some small active nodules may not even be detected on PET and for nodules that are 3-4 mm in diameter, to detect the 28% increase in diameter (representing one doubling in size) may require waiting for several doublings to occur before the growth rate can actually be assessed. On the other hand, the smaller the lesion the more likely it is to be benign.

In reply, it was mentioned that in the algorithm presented, the plan for these small nodules would be to observe them. An additional problem is that pulmonary nodules can be very deeply placed in the lung in a position where they can not be removed. This leads to the issue of what is actually going to be done for these deep nodules and the debate that if one nodule is going to be left behind why not all.

It was clarified that there is an important distinction between tumour cell doubling and volume doubling (seen on X-rays and CT scans) and that these are not the same. It was highlighted that when a sphere doubles in size, it does not double in diameter. As nodules are spherical, the doubling in volume size of a nodule is not accompanied by a doubling of its diameter.

- Patient follow-up

There was discussion as to the implications of being able to follow patients enrolled in a screening study. It was pointed out that if patients remain in the study and are cooperative that they can be followed. For such patients, if a nodule is not biopsied right at the start then the patient can be followed with a program of assessment at three, six, nine, 12 months and so forth out to two years. The risk is that the patient leaves the study and is not followed-up.
The Economics of Screening by Helical CT Scans

Christine Stone, Public Health and Development Division, Department of Human Services, Melbourne, Victoria, 3001.

Overview
The presentation discussed economic modelling that can be undertaken to assess screening programmes for disease. The criteria required for an ‘Evidence Based Marginal Analysis’ were described including, cost-effectiveness, quality of evidence, equity implications, public health significance, acceptability and feasibility. These criteria were applied to helical CT screening for lung cancer using data from two previous studies (Japanese and US). Issues relating to health service utilisation and costs, complications of screening and criteria for benefit of screening were also discussed.

Abstract
The UK National Screening Committee in their second report published as an appendix The Criteria for appraising the viability, effectiveness and appropriateness of a screening program. In it they identify 19 criteria that should be met before screening for a condition to be initiated and group them under headings: the condition, the test, the treatment and the screening programme.

At the same time, an economic tool, Program Budgeting Marginal Analysis (PBMA), was being trialed to assist the Commonwealth with priority setting for cancer control in Australia. The economic protocol developed for that process has many parallels with the UK Screening Criteria. It includes reviews of the best level evidence in the Australian context, on the condition, the intervention, the health benefit, the health service utilisation and their costs, the cost effectiveness ratio, level of evidence, equity issues, acceptability and feasibility. This protocol facilitates clear, consistent comparisons between quite diverse interventions.

This protocol could be adapted to evaluate helical CT scanning. The results could be compared to interventions evaluated as part of the PBMA Trial such as the National Tobacco Campaign (primary prevention of lung cancer) or Population Screening for Colorectal Cancer using Faecal Occult Blood Test (another screening program).

However there are many questions that need to be answered before an economic evaluation can be done let alone a screening program be implemented. What is the effectiveness of the program? Has the mortality reduction from the intervention been proven? Who will be screened? How will they be screened? Are the normal treatment pathways known and how will they change with the introduction of a screening program. Has the primary prevention program been implemented as far as possible?

This paper will outline the important criteria for the evaluation of a screening program, highlight some of the current unknowns in relation to helical CT scanning and make comparisons with previous evaluations.
**Discussion**

Issues discussed were as follows:

- **Use of high resolution helical CT scans**

There was discussion as to the use of high-resolution versus low-dose helical CT scans in the follow-up of patients in proposed Australian screening studies. The point was raised that high-resolution helical CT scans would be unlikely to be used in the follow-up of nodules detected by low-dose helical CT scanning, rather follow-up would be conducted using a standard CT. This has implications for the costing and potential impact of a proposed study.

- **Cost-effectiveness**

The point was raised that if incremental cost-effectiveness is examined, particularly from the point of view of making subsidy decisions, there have to be appropriate end points such as overall mortality gain (not just disease-specific mortality gain) and quality of life in the people being screened. In addition, for a screening study in which screening (of whatever description) forms the intervention arm, there should be an appropriate comparator in the control population. For example, patients who are smokers and who receive standard management in general practice.

It was mentioned that the proposed studies appeared expensive and that it was doubtful whether they would achieve an acceptable cost-effectiveness ratio. The suggestion was made that in terms of allocative efficiency, for avoiding lung cancer and improving mortality, it might be more worthwhile to invest funds into smoking cessation programs as these have an attractive cost-effectiveness ratio. This was acknowledged, however, it was pointed out that there is still a need to do something for people who already have lung cancer or potentially may develop lung cancer and how to optimise the benefit for these people needs to be investigated.

It was commented that entrepreneurial members of the medical profession could start to offer scans for lung disease. Thus, one incentive for undertaking a trial to determine what exactly are the benefits of screening (despite the argument that it is economically unattractive) is to provide evidence-based practice and a reasonable and sound argument to counter such potential entrepreneurial activities.

- **Targeting high-risk subjects**

There was discussion as to what are the implications for the economic modelling if the target group was altered from just smokers to subjects whose incidence of lung cancer is very much higher. Namely, subjects who are smokers (or have been exposed to cigarette smoke in the workplace) and have been exposed to asbestos. It was discussed whether this is a group in whom screening might be beneficial from a cost-effectiveness point of view and whether it was possible to model the incidence of lung cancer needed to demonstrate that screening in this group is worthwhile.

In reply, it was indicated that the modelling is possible if the data are available, however, a difficulty here is that the level of evidence available is very poor. In addition, subjects in this group may have fewer resectable cancers, which could reduce the effectiveness of such a programme.
• Harms and benefits – need for further information

The point was made that the economic modelling presented had been put together using only a limited amount of information and that it would be valuable to obtain further information on the harms and benefits of screening for lung cancer using helical CT scans. In addition to the harms of the scan itself, there could be complications due to the increase in invasive diagnostic tests and complications associated with lung cancer treatment. It was commented that there are people who are resistant to screening and to be able to enrol them in a study, there is a need to convince them that the harms are not going to be greater than the benefits.

It was discussed that one group for whom the harm may be particularly great is the person who continues to smoke and continues to be screened as the risk of the screening (X-rays, CT scans) add to the risks of the ongoing smoking. The benefits of screening are likely to be less in committed smokers.

• Former smokers

The question was then raised as to how the modelling would appear if the subjects selected were recently ceased smokers. This is a group for whom the risks of developing lung cancer over the next five years are still significant. There was discussion as to what would happen if screening was conducted in this group for a finite period of time until the risk of developing lung cancer becomes statistically low. As all cause mortality from other smoking-related disease is also going to decrease, this may be a group in whom screening is the most-cost effective.

This raised the issue that there is debate around denying a programme to a person who has not given up smoking. There was also discussion that there is a need to offer something to people who have stopped smoking, as this is an incentive to get them give up the first place. At present people are being encouraged to stop smoking but there is no secondary tumour prevention available. It was felt that this provided a good argument to at least offer these people screening – if it is known that it is beneficial and not harmful.
In the audience discussion that took place after the presentations, those attending the workshop were asked to address the question of the meeting, namely ‘Where does Australia go to from here?’ The discussion was approached under two broad headings, the issue of whether Australia should conduct its own randomised controlled trial to evaluate helical CT screening for lung cancer or whether a study of some description other than a randomised controlled trial should be considered.

With respect to current activities that are evaluating helical CT scanning as a screening technique for lung cancer, it was mentioned there are several international randomised trials (either current or planned) and that these trials are expensive and that it will take some time before the results will be known.

Three possible outcomes from the international trials were highlighted:

1. They could show a clear benefit (even in economic terms), with resulting pressure to implement the findings in Australia when they are known. This has implications for various factors including training, competence and workload.

2. They could show no benefit.

3. They could show something in between, such as a clinical benefit but questions about cost-effectiveness. This raises the issue of whether the international results (clinical, economic and social) can be readily translated to the Australian population.

To stimulate debate a number of specific questions were put to the audience for their consideration and comment.

**Questions put forward for discussion included:**

- Should Australia wait for the results from the international trials and then apply the results, and is this is sufficient?

- Should Australia be doing something while waiting for the results of the international trials?

- Should Australia explore possibilities of joining in with an international trial?

- Should Australia conduct its own randomised controlled trial, either designed to be complementary to an international trial or as a stand alone trial?
Audience Discussion – Issues Raised

Need for an Australian study

- There is need for an Australian study of some description to provide important local information as to the costs and benefits of screening in the Australian setting.

- Data from the international studies will not be available for many years and we need to have local information and local strategies to deal with Australians who are at risk.

Funding

- An Australian randomised controlled trial would be very expensive. Australia is a smaller country in terms of population that other countries planning to undertake randomised controlled trials of helical CT screening, however, the numbers of people needed for such a trial here are no different from larger countries. If a randomised controlled trial is to be proposed in Australia a clear idea of funding sources would be required.

- While there are precedents for international funding of research, it is unlikely that international organisations would fund part of a multi-centre trial within Australia.

Need for Australian data

- There is need for Australian data on pulmonary nodules including prevalence rates, characteristics and natural history. Prevalence rates for pulmonary nodules may differ geographically within the country and within different populations.

- Information on pseudo-disease is important and needed, including the need to identify which pulmonary nodules are likely to be lethal.

- There was variance of opinion on the management of pulmonary nodules, raising the issue of whether a trial of nodule management is needed and could a pilot program provide useful outcome data, although without randomisation an ultimate answer on efficacy will not be given.

- There is need for consideration that if international studies show benefit can the results be automatically applied to the Australian population.

Economic assessment

- As data from the randomised controlled trials of helical CT screening are not yet available, the intervention effect size for a modelled economic evaluation is not known. A suggested alternative approach is to take an acceptable incremental cost-effectiveness ratio and work back through the model to identify what effect size would be needed from the screening to achieve this. This would then allow judgement as to whether the intervention effect size is feasible.
Audience Discussion – Issues Raised

Potential target groups

- The target groups in whom to concentrate potential screening studies need to be identified. It was suggested that screening activities should be concentrated in subjects who are at the highest-risk, as this may be where screening has the greatest benefit.

- When considering target groups, there was mention that it should be remembered that if the ultimate outcome is to have patients undergo curative surgery, that the group screened must still be fit to undergo resection of screen-detected nodules.

Molecular markers and biomarkers

- Can biomarkers offer a less invasive first-line screening test? This was discussed, however, at present it is too early to assess this.

- Molecular markers have the potential to identify individuals at risk of lung cancer, however, at present available treatment for lung cancer requires lesions to be anatomically located. Thus, currently this technology can complement helical CT scanning not replace it.

Public interest

- Defacto screening for lung cancer by chest X-ray is already occurring in high-risk subjects (smokers) and will continue to occur due to community pressure.

- There is significant public interest in the topic of lung cancer screening and there is pressure to come up with a rational approach to screening in high-risk people, in particular those who have smoked heavily and been exposed to asbestos.

- Issue of public interest and the industrial issue is important and may have funding implications.

Study design

- Can a randomised controlled trial be equalled by a study with a one-arm design such as the ELCAP study? This would not have the same outcomes, but will provide local information, has cost benefits and raises issue of whether information on efficacy can be obtained this way.

International trials

- The possibility of joining in an international study should not be ruled out.

- Regarding the question as to whether a population-based screening programme using helical CT scanning is going to ultimately alter the mortality of lung cancer, Australia may have to wait for the results of the large international trials. An interim analysis could provide some momentum.


**Audience Discussion – Issues Raised**

**Potential Australian activities**

- While there is a legitimate case for waiting for the results of the international trials, there is also merit in exploring ways that Australia could answer some of the questions that need to be addressed on a local level. There may be ways forward for obtaining funding for something other than a large randomised controlled trial.

- What questions would a pilot trial in Australia answer and should an Australian study be a multi-centre program or should different centres conduct different studies.

**Role of the NCCI**

- The NCCI indicated that it would be willing to further support activities relating to the assessment of helical CT screening for lung cancer in Australia, in what ways it can. It was clarified that the NCCI is not a funding source for specific trials.

**Proposals**

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<td>1. That a multi-centre pilot study should be established in Australia. This could provide local information and will bring together expertise.</td>
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<td>2. That a detailed economic analysis should be undertaken to assess the expected costs and mortality benefits of helical CT screening.</td>
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<td>3. That a further meeting should be convened to bring together representatives from each state to review what has been discussed and take it forward from there.</td>
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<td>4. That support should be given for a screening trial to detect pulmonary lesions in those patients at highest risk.</td>
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**General Comments**

The meeting was thought to be a valuable exercise. The NCCI indicated that it would be willing to provide further assistance in this area, although the point was made that the NCCI is not a funding source. There was recognition that lung cancer is an important disease and that Australia should be active in some form in furthering the screening issue, rather than just waiting for the results of the international trials. The specific nature of what should be undertaken remains to be determined. There was a general feeling, although consensus was not unanimous, that a major Australian randomised trial was not the best way forward. In addition, there was a general feeling that different centres would be prepared to cooperate.

**Note:** The above comments reflect the overall impressions from the meeting.