

SECTION II

PREVENTION AND

DIAGNOSIS

2. PREVENTION AND SCREENING

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2.1 SMOKING CESSATION

Smoking is the largest single preventable cause of death and disease including lung cancer. Consequently, tobacco control measures, including taxation and price policy, advertising restrictions, public information, health promotion and smoking cessation support, are pivotal in reducing the burden of disease from smoking. The Ministerial Council on Drug Strategy endorsed an action plan under the National Drug Strategic Framework, the National Tobacco Strategy (NTS) 1999 to 2002–03, in June 1999. This is reproduced in Appendix 6.

Guidelines for smoking cessation have recently been published in Britain consisting of guidelines for clinicians, health administrators and managers in a complete version¹ in conjunction with a cost-effectiveness guidance² as well as a shortened version³. These were based on systematic reviews by the Cochrane Tobacco Addiction Review Group and the US Agency for Health Care Policy and Research (AHCPR—www.ahcpr.gov)⁴.

Similarly, the US Public Health Service Report *Treating tobacco use and dependence: a clinical practice guideline*⁵ has been published recently and summarised in a consensus statement⁶. These were produced by a panel charged with identifying effective, experimentally validated tobacco dependence treatments and practices and highlight differences from the original AHCPR 1996 *Smoking cessation clinical practice guideline*.

Overall the essential features of smoking cessation advice can be summarised as the five A's:

- Ask (about smoking at every opportunity)
- Advise (all smokers to stop) – advice re cannabis see Chapter 1, section 1.3
- Assess (willingness to quit)
- Assist (the smoker to stop)
- Arrange (follow-up).

Further guideline details including effective counselling and behavioural techniques, pharmacotherapy, enhancing motivation to quit, brief strategies for preventing relapse, and intensive smoking cessation intervention components, are published in the aforementioned references. In addition, there are specific guidelines in relation to hospital patients, pregnant smokers, young people, low income smokers, sex, weight gain, training for health professionals, telephone help line workers and health administrators. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists has published a statement regarding women and smoking, including information on smoking and pregnancy (see www.ranzcog.edu.au under College Statements).

In addition, about 20 systematic reviews on smoking cessation are available in the Cochrane Library analysing randomised controlled trials of smoking cessation with at least six months follow-up. The Cochrane Library has recently reviewed the findings on the effectiveness of available interventions⁷, which are briefly summarised below.

INTERVENTIONS FROM DOCTORS AND NURSES

Data on smoking cessation advice from a medical practitioner has been collected from 34 trials, including over 27 000 smokers. In some trials, subjects were at risk of specified diseases (smoking related chest disease, diabetes, ischaemic heart disease), but most were from unselected (convenience sampling) populations. The most common setting for delivery of advice was primary care, but others included hospital wards and outpatient clinics, and industrial clinics⁸. Pooled data from 16 trials of brief advice versus no advice (or usual care) revealed a small but significant increase in the odds of quitting (OR 1.69, CI 1.45–1.98). Direct comparison of intensive versus minimal advice showed a small advantage of intensive advice (OR 1.44, CI 1.23–1.68). The only study of the effect of smoking advice on mortality found no statistically significant differences in death rates at 20 years follow-up. The reviewers concluded that simple advice has a small effect on cessation rates.

Nurses are also effective. A Cochrane review of 16 studies comparing nursing delivered smoking cessation interventions to a control or usual care, found intervention to significantly increase the odds of quitting (OR 1.50, CI 1.29–1.73). There was, however, heterogeneity between the study results, but pooling using a random effects model did not alter the estimate of effect. The authors concluded that the results indicate that smoking cessation advice and counselling given by nurses to their patients is supported by evidence that these interventions can be effective⁹.

BEHAVIOURAL AND PSYCHOLOGICAL INTERVENTIONS

Both individual counselling and group therapy increase the chances of quitting^{10,11}.

Fifteen studies in an updated Cochrane review on individual behavioural counselling for smoking cessation compared individual counselling to a minimal intervention. Four studies compared different types or intensities of counselling. It was concluded that individual counselling was more effective than control. The odds ratio (the ratio of part to the remainder: it is used to express the chance that a particular outcome will occur) (OR) for successful smoking cessation was 1.62 (CI 1.35–1.94). The authors failed to detect a greater effect of intensive counselling compared to brief counselling (OR 0.98, CI 0.61–1.56)¹¹.

Group therapy offers individuals the opportunity to learn behavioural techniques for smoking cessation and to provide each other with mutual support. The Cochrane review suggested that there was reasonable evidence that groups are better than self help and other less intensive interventions, however, they may be no better than advice from a health care provider¹⁰. There is not enough evidence on their effectiveness compared to intensive individual counselling. From the point of view of the consumer, who is motivated to make a quit attempt, it is probably worth joining a group if one is available, as it will increase the likelihood of quitting. Group therapy may also be valuable as part of a comprehensive intervention that includes nicotine replacement therapy (NRT), which is frequently used as a component of smoking cessation strategies and includes

nicotine gum, transdermal patch, nicotine nasal spray, nicotine inhaler and nicotine sublingual tablets/lozenges, designed to replace the nicotine that can be obtained from tobacco smoking.

Twenty-four mainly small trials studied aversion therapy consisting of pairing the pleasurable stimulus of smoking to an unpleasant stimulus. A Cochrane review concluded that the existing studies do not provide sufficient evidence to determine either the efficacy of rapid smoking, where subjects are encouraged to smoke at an increased rate (see Glossary), or whether there is a dose-response to aversive stimulation. Milder versions of aversive smoking seem to lack efficacy¹².

Two studies of silver acetate, which causes an unpleasant taste when combined with cigarettes, showed no evidence of benefit, although confidence intervals were wide (OR 1.05, CI 0.63–1.73)¹³. Any effect of this agent is therefore likely to be smaller than NRT.

SELF HELP

Self-help materials include written leaflets, manuals, audiotapes, videos, and computer programs that may be given as an adjunct to brief advice or without any personal contact.

A Cochrane review studied 51 randomised trials of smoking cessation with follow-up of a minimum of six months, where at least one arm tested a self-help intervention (structured programming for smokers trying to quit without intensive contact with a therapist)¹⁴. Thirty-two trials compared self-help materials to no intervention or tested materials used in addition to advice. In 11 trials in which self help was compared to no intervention there was a pooled effect that just reached statistical significance (OR 1.24, CI 1.07–1.45). Four further trials failed to find evidence of benefit for either adding self-help materials to face-to-face advice, or to NRT. There was evidence from 14 trials using materials tailored for the characteristics of individual smokers that such personalised materials were more effective than standard manuals (10 trials, OR 1.36, CI 1.13–1.64) or no materials (three trials, OR 1.80, CI 1.46–2.23). A small number of trials failed to detect benefit from using additional materials or targeted materials. Thus, standard self-help materials may increase quit rates compared to no intervention, but the effect is likely to be small.

Telephone services can provide information and support for smokers. Counselling may be provided proactively or offered reactively to smokers who call smoking cessation help-lines. A recent Cochrane review of randomised or quasi-randomised controlled trials in which proactive or reactive telephone counselling to assist smoking cessation was offered to smokers or recent quitters, found that proactive telephone counselling can be effective compared to an intervention without personal contact¹⁵, although the size of effect is uncertain.

PHARMACOLOGICAL INTERVENTIONS

NICOTINE REPLACEMENT THERAPY

Nicotine replacement is available as chewing gum, transdermal patch, nasal spray, inhaler, sublingual tablet and lozenge. A Cochrane review identified 108 trials: 94 with a non-NRT control group. The odds ratio for abstinence with NRT compared to control was 1.73 (CI 1.62–1.85)¹⁶. The odds ratios for the different forms of NRT were 1.66 for gum, 1.76 for patches, 2.27 for nasal spray, 2.08 for inhaled nicotine and 1.73 for nicotine sublingual tablet. These odds were largely independent of the duration of therapy, the intensity of additional support provided or the setting in which the NRT was offered. In highly dependent smokers there was a significant benefit of 4mg gum compared with 2mg gum (OR 2.67, CI 1.69–4.22). There was weak evidence that combinations of forms of NRT are more effective. Higher doses of nicotine patch may produce small increases in quit rates. Only one study directly compared NRT to another pharmacotherapy, in which bupropion was significantly more effective than nicotine patch or placebo.

The conclusion was that all of the commercially available forms of NRT (nicotine gum, transdermal patch, nicotine nasal spray, nicotine inhaler and nicotine sublingual tablets) are effective as part of a strategy to promote smoking cessation. They increase quit rates approximately 1.5 to two-fold regardless of setting. The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the smoker. Provision of more intense levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT.

ANTIDEPRESSANTS AND ANXIOLYTICS

Although anxiolytics have not yet been shown to be effective, there is evidence that some antidepressants can help quitting. A Cochrane review¹⁷ considered randomised trials comparing antidepressant drugs to placebo or an alternative therapeutic control for smoking cessation. There was one trial each of moclobemide, sertraline and venlafaxine, two of fluoxetine and nortriptyline, and five trials of bupropion, one of which tested long-term use to prevent relapse. Nortriptyline and bupropion both increased cessation. In one trial the combination of bupropion and nicotine patch produced slightly higher quit rates than patch alone. Consequently, some antidepressants (nortriptyline and bupropion) can aid smoking cessation. For bupropion, pooled results of four trials with 12-month abstinence rates and three with six-month rates gave an estimated odds ratio of 2.54 (CI 1.90–3.41). It is not clear whether these effects are specific for bupropion, or would occur with any antidepressant.

OTHER PHARMACOLOGICAL THERAPIES

The antihypertensive clonidine shares some pharmacological effects with bupropion and tricyclic antidepressants. A Cochrane review of six trials showed evidence of efficacy (OR 1.89, CI 1.30–2.74), but there were potential sources of bias, and its usefulness is limited by the side effects of sedation and postural hypotension¹⁸.

The nicotine antagonist mecamylamine has been investigated as a cessation aid in combination with nicotine replacement. Two small studies show that mecamylamine, started before cessation and continued afterwards, may help smoking cessation, and that a combination of mecamylamine and nicotine replacement, started before cessation, may increase cessation rates achieved with nicotine replacement alone²⁰. However, the reviewers concluded that the results require confirmation in larger studies before the treatment can be recommended clinically.

Lobeline is a partial nicotine agonist derived from the leaves of an Indian tobacco plant and has been used in proprietary smoking remedies. A Cochrane review found no trials with six months of follow-up²¹.

Guidelines – Strategies to Help People Stop Smoking	Level of Evidence	Refs
Effective interventions include advice from doctors, structured interventions from nurses, and individual/group counselling.	I	8,9,10,11
Generic self-help materials are no better than brief advice, but more effective than doing nothing.	I	14
Personalised materials are more effective than standard materials.	I	14
All currently available forms of nicotine replacement therapy are effective.	I	16
Bupropion and nortriptyline increase effectiveness as evidenced by quit rates.	I	17
Personalised smoking cessation advice for inpatients together with at least one month of follow-up increases quit rates.	I	24

OTHER THERAPIES

A Cochrane review of 22 studies concluded that acupuncture was not superior to sham acupuncture in smoking cessation at any time point²². The odds ratio for early outcomes was 1.22 (CI 0.99–1.49); the odds ratio after six months was 1.50 (CI 0.99–2.27) and after 12 months was 1.08 (CI 0.77–1.52). Similarly, when acupuncture was compared with other anti-smoking interventions, there were no differences in outcome at any time point. Acupuncture appeared to be superior to no intervention in the early results, but this difference was not sustained. The results with different acupuncture techniques do not show any one particular method (i.e. auricular acupuncture or non-auricular acupuncture) to be superior to control intervention.

Another Cochrane review considered nine studies of hypnotherapy compared with 14 different control interventions²³. There was significant heterogeneity between the results of the individual studies, with conflicting results for the effectiveness of hypnotherapy compared to no treatment or to advice. There was no evidence for an effect of hypnotherapy compared to rapid smoking or psychological treatment. The reviewers concluded “we have not shown that hypnotherapy has a greater effect on six month quit rates than other interventions or no treatment”.

Existing evidence does not show a clear benefit for exercise in smoking cessation²⁴. The meta-analysis studied eight trials, six of which had fewer than 25 people in each treatment arm. Only one of the eight trials offered evidence for exercise aiding smoking cessation, all but one of the other trials were too small to exclude reliably an effect of intervention. Trials are needed with larger sample sizes, equal contact control conditions, tailored and lifestyle exercise programs and measures of exercise adherence.

Guideline – Strategies that do not help people stop smoking	Level of Evidence	Refs
Acupuncture, hypnotherapy, aversion therapy, immunotherapy and exercise have not been shown to effectively increase quit rates.	I	21,22, 23,24

HOSPITAL ADMISSIONS

An admission to hospital provides an opportunity to help people stop smoking. A Cochrane review found that intensive intervention (inpatient contact plus follow-up for at least one month) was associated with a significantly higher quit rate compared to control (OR 1.82, CI 1.49–2.22). There was no strong evidence that clinical diagnosis affected the likelihood of quitting¹⁹.

CONCLUSIONS

Many factors including societal attitudes, legislation and public health measures influence tobacco use. Many smokers can give up without clinical intervention. Nonetheless, it is clear that effective strategies are available and should be offered to all smokers who express a desire to quit. Effective interventions include advice from doctors, structured interventions from nurses and individual/group counselling, and include:

- Motivational interviewing⁵
- Concise, brief non-judgemental advice
- Arrange follow-up⁶
- Enlist support⁵
- Pharmacotherapy¹⁶
- Refer to QUIT line
- Flagging smoking status on case notes of all attending patients⁵
- Targeted to stage of change¹¹
- Use the five A's⁵.

2.2 NUTRITION

Accurate measurement of the relationship between lung cancer and diet presents a number of difficulties. These include methodological problems in measurement of nutrient intake, which ideally should be measured at different points in time prior to the development of cancer. The history of smoking and exposure to environmental tobacco smoke is also required, but is often lacking in sufficient detail. As a result, studies have not always produced consistent results. Ziegler et al undertook a comprehensive review of the literature on nutrition and lung cancer, which was completed in 1995²⁵. The following section outlines their conclusions.

Recent studies have generally shown that lung cancer risk is reduced at high levels of vegetable and/or fruit consumption, or at high levels of intake of carotenoids or vitamin C, which are markers of vegetable and fruit intake²⁶⁻⁴⁹.

The specific mechanisms of this relationship have not yet been elucidated, although a large number of compounds found in edible plants have been shown to inhibit experimental mutagenesis and carcinogenesis in animals^{50,51}. Some micronutrients, such as the provitamin A carotenoids, vitamin C, vitamin E and selenium may inhibit carcinogenesis by functioning as antioxidants^{52,53}. However, while observational and biochemical studies indicated a protective effect for beta-carotene (a provitamin A carotenoid)^{28,29,30,31,32,34,35,54,55,56,57,58} and led to the intervention trials described in section 2.3, evidence for a protective effect of vitamin C, vitamin E and selenium has been less conclusive^{27,28,30,31,32,34,35,36,37,41,43,45,47,56,59,60,61,62,63,64,65,66}.

Study populations are generally divided into quintiles or quartiles according to their vegetable and/or fruit intake and the risk of lung cancer is compared across these groups. The smoking-adjusted relative risk (RR) of lung cancer in the highest quintile compared to the lowest quartile tends to be in the order of 1.3–2.0^{67,68,69,70}.

In some studies, the relationship between fruit and vegetable consumption and lung cancer has varied according to sex, race, smoking history and histologic subtype^{26,32,38,43,71,72}. While these observations may be genuine, it is possible that they are attributable to small numbers in specific subgroups, methods of analysis or chance.

Dietary fat has been identified as a tumour promoter in experimental animals and this has led to studies of its relationship with lung cancer⁷³. Some studies have provided support for this hypothesis but there have been a number of inconsistencies, particularly regarding the size of the association. The relevant component(s) of dietary fat (cholesterol, total and saturated fat) have also not been identified²⁵.

Since 1995, further studies on the relationship between nutrition and lung cancer have been completed, but have not altered the conclusions reached above^{72,74,75,76,77}. With regard to carotenoids, recent research by Michaud et al found that alpha-carotene and lycopene were significantly associated with a lower risk of lung cancer, rather than beta-carotene, lutein and beta-cryptoxanthin⁷⁸. Further studies will be required to confirm this conclusion.

Therefore, while evidence still points to the conclusion that increased vegetable and fruit intake decreases risk of lung cancer, the specific mechanism(s) by which this occurs and the specific nutrients involved have yet to be determined.

2.3 CHEMOPREVENTION

Chemoprevention can be defined as the use of specific natural or synthetic agents to prevent, suppress or reverse carcinogenesis before the development of invasive malignancy. A fundamental tenet upon which its use is based, is the field cancerisation hypothesis in upper aerodigestive tract malignancy, which predicts that diffuse epithelial injury occurs as the result of inhaled carcinogens. Clinical evidence for field carcinogenesis comes from observing premalignant lesions and multiple primary tumours⁷⁹ and is reinforced by molecular studies^{80,81}.

CHEMOPREVENTION FOR LUNG CANCER

Two large randomised primary chemoprevention trials in lung cancer have studied individuals at increased risk for the development of lung cancer as the result of smoking or asbestos exposure.

The Alpha-Tocopherol Beta Carotene (ATBC) trial randomised 29 133 Finnish male smokers, aged 50–69 years, in a 2 x 2 factorial design of alpha-tocopherol (50mg/day) and beta-carotene (20mg/day) to (1) beta-carotene alone, (2) alpha-tocopherol alone, (3) beta-carotene plus alpha-tocopherol, or (4) placebo. After dietary supplementation for five to eight years, those given beta-carotene (alone or with alpha-tocopherol) had a higher incidence of lung cancer (RR 1.18, CI 1.03–1.36) and higher total mortality (RR 1.08, CI 1.01–1.16). This effect appeared to be associated with heavier smoking and alcohol intake^{82,83}. Supplementation with alpha-tocopherol produced no overall effect on lung cancer (RR 0.99, CI 0.87–1.13).

The US Beta-Carotene and Retinol Efficacy Trial (CARET) randomised 18 314 smokers, former smokers, and asbestos-exposed workers to beta-carotene (30mg/day) plus retinyl palmitate (25 000IU/day) or placebo. The trial was terminated early as it also found a harmful effect of beta-carotene over that of placebo: increased lung cancer (primary endpoint) incidence (RR 1.28, CI 1.04–1.57) and total mortality (RR 1.17; CI 1.03–1.33). The possibility of excess lung cancer incidence being associated with higher alcohol intake was considered^{84,85}.

The two studies thus suggest that pharmacological doses of beta-carotene may increase lung cancer risk in relatively heavy smokers, that is, individuals at high risk for developing lung cancer. Lung cancer risks were not increased in subsets of moderate-intensity smokers (less than one pack per day) in the ATBC study, or in former smokers in the CARET study. Importantly however, those with higher pre-intervention serum or intake levels of beta-carotene had a lower lung cancer risk, supporting the premise that dietary vegetables and fruit may prevent the development of lung cancer.

CHEMOPREVENTION FOR MULTIPLE CANCERS

The randomised, double-blind, placebo-controlled Physicians' Health Study of 22 071 male physicians aged 40–84 years studied the effects of beta-carotene and aspirin in cancer and cardiovascular disease. In this trial, 12 years of supplementation with beta-carotene (50mg on alternate days) had no effect on overall risk of cancer or of lung cancer among current (11% of study population) or former (39% of study population) smokers⁸⁶.

In the Women's Health Study, 39 876 female health professionals aged 45-years and over were randomised to aspirin, vitamin E and beta-carotene in a double blind, placebo-controlled design. The beta-carotene (50mg on alternate days) component was terminated early, but there was no evidence of benefit or harm on cancer risk including lung cancer after a limited treatment duration (median 2.1 years) at a median follow-up of 4.1 years⁸⁷.

REVERSAL OF PREMALIGNANCY

Morphological changes in the bronchial epithelium, for example metaplasia and dysplasia, have been used as endpoints in some chemoprevention studies. An early uncontrolled trial found that six months of etretinate (25mg/day) was effective in reversing squamous metaplasia in biopsy specimens from heavy smokers⁸⁸. However, a randomised chemoprevention trial found that isotretinoin (1mg/kg/day) was no better than placebo at reversing squamous metaplasia in bronchoscopic biopsies⁸⁹.

Similarly, a randomised trial of etretinate (25 mg/day) was no different from placebo in reducing sputum atypia after six months treatment in 138 smoking subjects⁹⁰. A placebo-controlled randomised lung cancer chemoprevention trial of beta-carotene (50mg/day) plus retinol (25 000IU every other day) in approximately 750 US male asbestos workers also found no difference in the primary endpoint of prevalence of sputum atypia after a median intervention period of 58 months⁹¹.

These studies suggest that retinoids have minimal or no effect on metaplasia, a process which may vary spontaneously and with smoking cessation. Some have proposed that retinoids may be active in later stages of preneoplastic lung carcinogenesis but this remains to be tested.

PREVENTION OF SECOND PRIMARY LUNG CANCERS

The lifetime risk of second primary tumours (SPTs) following early stage lung cancer may be as high as 20–30%. These observations have provided the impetus to study chemoprevention for second primary lung cancer.

Initial favourable results came from a small randomised study of high-dose retinyl palmitate (300 000IU/day), given in an adjuvant phase III trial following resection of Stage I NSCLC⁹². Although there was no statistically significant improvement in disease-free survival for the retinyl palmitate group, there was an improvement in terms of time-to-new-primary cancers in the field of prevention (lung, head and neck, bladder).

On the other hand, the European multicentre (EUROSCAN) study of 2 592 participants, consisting of a 2 x 2 factorial design to study the efficacy of retinyl palmitate (300 000IU daily for one year followed by 150 000IU for the second year) and 600mg daily of the antioxidant N-acetyl-cysteine (following head and neck or lung cancer), found no benefit in terms of survival, event-free survival or SPTs for these patients, most of whom were former or current smokers⁹³.

The recent randomised, double-blind, placebo-controlled trial of low-dose isotretinoin (30 mg/day) in preventing second primary tumours following Stage I NSCLC concluded that isotretinoin treatment did not improve the overall rates of SPTs, recurrences, or mortality⁹⁴. Secondary multivariate and subset analyses suggested that isotretinoin was harmful in current smokers and beneficial in never smokers.

CONCLUSION

Chemoprevention strategies to date have been disappointing for the primary prevention of lung cancer. There is an increased risk of lung cancer from pharmacological doses of beta-carotene in heavy smokers. For the prevention of second lung cancers, despite an initial promising study, a larger study failed to show any benefit for retinyl palmitate and/or N-acetyl cysteine. There are several currently ongoing studies of newer chemopreventative strategies which may provide additional information in the future^{95,96,97}.

Guideline – Chemoprevention Strategies in Lung Cancer	Level of Evidence	Refs
Data do not support the use of currently reported chemoprevention strategies in lung cancer.	II	86,87,88, 89,90,91,92, 93,94

Guideline – Dietary Supplementation with Beta Carotene	Level of Evidence	Refs
Diet supplemented with pharmacological doses of beta-carotene increases the risk of lung cancer in heavy smokers.	II	82,83, 84,85

2.4 CASE FINDING

Some experts distinguish between mass screening and case finding⁹⁸. Case finding has been defined as the examination or testing of a particular person who seeks clinical evaluation out of concern about a disease or defect or because of symptoms⁹⁹. Some clinicians recommend case finding on an individual basis particularly for very high-risk individuals such as smokers with additional risk factors (airway obstruction or a history of asbestos exposure)⁹⁹. At present there is insufficient evidence to support this approach. However, if and when the issue of screening arises in the context of a consultation, it would be reasonable for medical practitioners to exercise their clinical judgement and make decisions about the role of screening on a case by case basis. Any patient offered screening in this context should be fully informed about the potential risks and benefits. Patients should be given information about the risk of false negative and false positive results and the risk of being diagnosed with ‘pseudodisease’¹⁰⁰.

2.5 SCREENING

INTRODUCTION

Currently, most lung cancers present at a stage when they are no longer potentially curable with surgical resection. Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (USA) show that of invasive lung cancers, 15%, 24%, 48% and 13% are staged as having localised, regional, distant and unstaged disease respectively¹⁰¹. Lung cancer screening offers the potential for tumours to be diagnosed at an earlier stage and this might lead to higher cure rates. Although primary prevention should continue to be the major focus of public health campaigns, in the near future the majority of lung cancer cases will be occurring among former smokers and there is a need to consider secondary prevention measures. Screening of high-risk individuals has previously been investigated in several randomised controlled trials^{102,103,104,105,106,107,108}. These studies were all conducted in the 1960s and 1970s and the findings have been summarised in a recent systematic review¹⁰⁹. The main conclusion that can be drawn from this review is that none of the lung cancer screening studies conducted to date have shown that screening alters the natural history of lung cancer. Because of limitations with previous studies further studies are being planned. Furthermore new screening tools such as helical (or spiral) computed tomography (CT) and biomarkers offer promise for the future.

CHEST RADIOGRAPHY

The major limitation of previous studies is that none of them included an unscreened control group. In the Mayo Lung Project, participants (male smokers) in the intervention group were offered four-monthly chest x-rays and sputum cytology examinations, while participants in the control group were advised to have an annual chest x-ray and sputum examination at the start of the study¹¹⁰. In a Czech study, participants (male smokers) in the intervention group were offered six-monthly chest x-rays and sputum cytology examinations for the first three years and annual chest x-rays for the last three years of the study. The control group were offered a chest x-ray and sputum cytology examination at baseline and after three years followed by annual chest x-rays for the last three years of the study¹⁰⁷. The results from extended follow-up of these studies have recently been reported^{111,112}. Both studies showed that more frequent screening was not associated with a reduction in lung cancer mortality. In fact, screening with chest x-rays more frequently than annually was associated with a slight increase in lung cancer mortality compared with annual or less frequent screening¹⁰⁹.

A multi-screening study currently being conducted in the USA has been designed to examine the efficacy of annual chest x-ray screening when compared with usual care. The PLCO (prostate, lung, colon and ovarian) cancer screening study is currently enrolling male and female subjects aged 55–74 years¹¹³.

Participants randomised to the intervention group will be offered an annual chest x-ray for three years. The control group will not be offered active screening. Participants in the intervention group will also be offered screening tests for colon, ovarian (females) and prostate (males) cancer. The primary outcome is disease specific mortality. The results are not expected until 2015.

SPUTUM CYTOLOGY

Two of the randomised controlled studies conducted in the 1970s were designed to assess whether sputum cytology at four monthly intervals would reduce lung cancer mortality when added to annual chest x-ray screening^{105,108,114}. Each study had an almost identical study design. Both enrolled smokers over the age of 45 years. The intervention groups were offered annual chest x-rays and four-monthly sputum cytology examinations. The control groups were offered an annual chest x-ray only. In both studies, the addition of sputum cytology to annual chest radiography was not associated with a reduction in lung cancer mortality, however, the sample size in these studies was relatively small and the studies had insufficient statistical power to detect more marginal reductions in lung cancer mortality¹⁰⁹.

Guideline – Population Screening for Lung Cancer	Level of Evidence	Refs
No forms of population screening for lung cancer, including regular chest radiography, with or without sputum cytology even in high-risk groups, have been shown to improve outcomes and screening is not recommended.	I II	108,111, 113,116 105,107, 110

LOW-DOSE HELICAL COMPUTED TOMOGRAPHY

Recent uncontrolled studies have shown that low-dose helical CT is a more sensitive screening tool than plain chest radiography^{116,117}. Although the findings of these studies are very promising, CT screening needs to be investigated in randomised controlled studies in order to determine whether early diagnosis and treatment will lead to a reduction in lung cancer mortality. Survival alone is not a reliable outcome measure in screening studies. Biases such as length-time, lead-time and overdiagnosis bias can produce an apparent improvement in survival even in the absence of a reduction in disease specific mortality¹¹⁵. A pilot randomised controlled trial comparing annual chest radiography with annual low-dose helical CT is currently being conducted in the USA and other studies are being planned¹¹⁵.

In comparison to chest radiography, helical CT provides axial images of the lungs and mediastinum, with superior contrast resolution unhindered by superimposition of anatomical structures¹¹⁸. As a result, CT has the potential to detect more lung cancers

when they are smaller and at an earlier stage. This is particularly relevant given the increasing proportion of adenocarcinomas, which are usually peripherally located in comparison to squamous cell carcinomas, which tend to be centrally located and less amenable to CT detection.

The effective radiation dose for a low-dose helical CT screening examination is 0.65 milliSieverts (mSv) in men and 1.1mSv in women. This compares with 5.8mSv for a conventional high-definition CT diagnostic examination^{119,120} and 0.015mSv for chest radiography. Because dose reduction in CT does not significantly decrease sensitivity for detection of small pulmonary nodules, low-dose helical CT has the potential to improve the early detection and prognosis of lung cancer. Clinical studies show that low-dose helical CT is a more sensitive screening tool for the detection of lung nodules and lung cancer than plain chest radiography^{115,121,122}.

Uncontrolled studies of low-dose helical CT have reported encouraging findings; these include studies in Japan, Finland, Germany and the USA, many linked to the US initiated Early Lung Cancer Action Program (ELCAP)^{116,123,124} (see also <http://ICScreen.med.cornell.edu>). These studies have assessed numbers and size of detected nodules, numbers of cancers detected and their size, stage, and surgical resectability. The results show that low-dose helical CT can detect lung cancers at a smaller size (less than 2cm in diameter) and earlier stage (58–100% Stage I) than chest radiography or current clinical practice (the mean diameter of the cancers detected in ELCAP was 8mm)¹²³. The potential benefit of this is shown by data from other studies indicating a significant survival benefit for Stage I lung cancers treated by lung resection, with up to about 70% five-year survival, in comparison to about 12% overall five-year survival for the ‘usual care’ outcomes¹²⁵.

Implementation of CT screening is critically dependent upon the availability of high-quality investigational procedures including fine needle aspiration (FNA) biopsies¹²⁵. In evaluating the potential benefits of any such project, any improvement in lung cancer outcomes must be balanced against the morbidity and mortality imposed by investigation of small lung nodules, a significant proportion of which will be shown not to represent lung cancers, but benign inflammatory or other non-neoplastic lesions. Nonetheless, it has been suggested that screening projects using helical CT show sufficient promise to be worth implementation on an experimental basis, concentrating upon high-risk groups¹²⁵. There are indications that the cost per life year gained may be acceptable, but these depend on the assumptions made about benefits¹²⁶. It has been suggested that patients with a smoking history of more than 20 cigarettes per day and greater than 25 fibres/ml-years of asbestos exposure, who are aged older than 50 years and who have greater than 10 years following commencement of the asbestos exposure and cigarette smoking are particularly suitable for evaluation of screening by helical CT¹²⁵.

The combination of low-dose helical CT and high-definition CT appears to provide good characterisation of lung cancers, with generally low rates of unnecessary surgical procedures. At this early stage of follow-up there is little available data on survival, and no data from controlled studies. Uncontrolled studies may not be able to determine if detection of small cancers will improve mortality rates, as distinct from post diagnosis survival rates, and the experience with conventional screening urges caution.

The studies (see National Cancer Control Initiative report, ‘Lung cancer screening by helical computed tomography’, available at NCCI website www.ncci.org.au) show high false positive rates for low-dose helical CT screening, although most positives can be resolved by further investigations without biopsy. No studies have yet examined how false positive results impact on the screenees’ quality of life. False negative rates for nodules also may be reasonably high; where both baseline and rescreening studies have been done between 36% and 66% of nodules detected on subsequent screening examinations were not seen on baseline scans. Technological advances and improved protocols may improve these figures, but wider use of the technique raises the issue of its performance by radiologists with less experience. The future availability of multi-slice/multi-detector helical CT scanners, and computer-assisted diagnosis and volumetrics, may significantly decrease the radiation exposure in a screening program. These advances may decrease the time for diagnosis of non-calcified nodules and decrease false negative rates, although these benefits may occur at the cost of higher false positive rates.

The uncontrolled studies of low-dose helical CT screening are controversial. Their proponents claim that the results in terms of tumour size, stage, operability, and patient survival will demonstrate the benefits of the technique¹²⁷. Critics argue that because of the potential biases of lead-time, prevalence-duration bias, and overdiagnosis, which have all been demonstrated in the earlier trials of conventional radiology, uncontrolled studies may never provide firm evidence of benefit and may be misleading^{119,128}.

One unanticipated benefit of ELCAP was a significant rate of smoking cessation (about 23%)¹²⁵. If this rate translates into long-term cessation, it would constitute an additional significant benefit and a major justification for implementation of an appropriate screening program based on helical CT.

Guideline – Helical CT Screening	Level of Evidence	Refs
In view of the limited information available on outcome, helical CT screening for lung cancer is not recommended except in the context of a well-designed clinical trial.	III-3	114,122, 124,126

There are several randomised trials that are ongoing or being established in the US and in Europe. These are also reviewed in the NCCI report¹²⁹.

BIOMARKERS AND FLUORESCENCE BRONCHOSCOPY

Methods for detecting altered gene expression in sputum or bronchoalveolar lavage samples have been developed and several of these allow the determination of a molecular diagnosis of cancer years before clinical presentation¹³⁰. For some of these tests the test performance characteristics are currently being investigated in prospective studies¹³⁰. Other methods being investigated for the early detection of lung cancer

include immunologic based screening of sputum and fluorescence bronchoscopy¹³¹. To date none of these methods have been used as a single screening technique in large randomised controlled population-based studies. Biomarkers are likely to be less accurate for the detection of small peripheral tumours but they might be a valuable complementary test to low-dose helical CT¹³².

OTHER METHODS FOR EARLY LUNG CANCER DETECTION

Recent research on potential approaches to earlier diagnosis of lung cancer includes studies of genetic markers, developments in sputum cytology, immunostaining, oncogene mutations detected by polymerase chain reaction assays, developments in conventional and fluorescent bronchoscopy including laser induced fluorescence endoscopy and optical coherence tomography, virtual bronchoscopy, and analysis of volatile organic compounds in breath samples. All of these are primarily research issues at present. They are briefly reviewed in the NCCI report.

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3. INITIAL ASSESSMENT AND PROGNOSTIC FACTORS

3.1 Appropriate referral for suspected lung cancer

3.2 Diagnosis of lung cancer

Chest x-ray and computed tomography scan

Sputum cytology

Fine needle aspiration and fiberoptic bronchoscopy

Fluoro-deoxy glucose (FDG) PET Scan

3.3 Staging lung cancer

Non-small cell lung cancer

 TNM staging

 T staging

 N staging

 M staging

Small cell lung cancer

 Staging system

 Staging procedures for SCLC

3.4 Prognostic factors

Non-small cell lung cancer

Small cell lung cancer

3.5 Follow-up

3.1 APPROPRIATE REFERRAL FOR SUSPECTED LUNG CANCER

Lung cancer has many presentations and occurs in individuals of varying ages and with a wide spectrum of comorbidities. When lung cancer is first suspected, the contribution of the tumour to reduced well-being and performance status of the patient may not be obvious, nor is the potential for a response to treatment always recognised. There is good Australian data that a significant number of patients with lung cancer do not receive a specialist opinion and are not considered for treatment¹. All people with suspected lung pathology should be referred to a specialist with expertise in the management of lung disease. Furthermore, patients with lung cancer should have access to a unit offering multidisciplinary care. Multidisciplinary care has been most useful in managing breast cancer, but remains unproven in managing lung cancer^{2,3}.

Guideline - Lung Cancer - Clinical Management	Level of Evidence	Refs
All individuals with suspected lung cancer should be referred to a specialist with expertise in the management of lung disease for an opinion.	IV	I

This includes patients who may appear physically or mentally unfit for further investigation or treatment. The specialist opinion will either endorse this approach, or will identify tumour-related effects on the patient's physical and mental state that may respond to specific tumour treatment or palliative care.

3.2 DIAGNOSIS OF LUNG CANCER

In most cases of suspected lung cancer it will be appropriate to confirm the diagnosis and establish the pathological subtype. Usually this is achieved with relatively non-invasive tests. Unless the diagnosis is confirmed histologically, there remains a possibility that the patient has some other condition which can be effectively treated.

CHEST X-RAY AND COMPUTED TOMOGRAPHY SCAN

The possibility of lung cancer is often raised by the presence of a solitary pulmonary nodule (SPN; lesion < 4cm) or lung mass (lesion > 4cm) on a chest x-ray. The challenge with SPNs is to diagnose all the lung cancers and to minimise invasive procedures in patients with benign lesions. Much research has been conducted in this area using chest x-ray, CT scanning and newer imaging and biological techniques.

Early lung cancer can present as an asymptomatic SPN detected on a chest x-ray or CT scan taken for other reasons. However, the majority of SPNs are benign. A summary of five large series of resected non-calcified SPNs showed that 54% were granulomas, 28% primary lung cancers, 7% hamartomas and 4% metastases⁴. Of 71 intrapulmonary coin lesions seen at The Prince Charles Hospital during 1982-1984, 48 were primary pulmonary malignancies and six were metastases. There were two cases each of tuberculosis, cryptococcosis, hamartoma and granuloma. Overall, 76% of the lesions were malignant and only 3% were tuberculous. These findings contrast with those from the same institution published 20 years ago, when malignancy comprised only 38% and tuberculosis 27% of lesions. Malignancy now seems to be the major cause of coin lesions in Australia. In this survey, 82% of SPNs that occurred in patients of over 50 years of age were malignant⁵.

The majority of individuals with lung cancer have symptoms at diagnosis⁶. Lung masses with associated clinical features are likely to be malignant and the next step is to obtain a tissue diagnosis in the least invasive manner (discussed below).

At present there is no specific protocol for investigating SPNs that can be recommended as a guideline. However, the following observations are relevant:

KEY POINTS:

These key points and a number of recommendations in this chapter have had evidence classified according to the Oxford Levels of Evidence for Diagnostic Tests, (see Appendix 7) and have been clearly identified -(O).

- **Lack of growth is better than any morphological feature on imaging. Therefore, comparison with previous x-rays is very useful. A lesion that has remained stable for two years may be benign⁷.**
- **Calcification is the single best morphological indicator of a benign lesion⁸ (II-O). CT detects calcification more accurately than chest x-ray⁹ (II-O).**
- **CT is the most sensitive imaging modality for identification of pulmonary nodules and is specific for the benign SPN with several diagnostic imaging findings. Specific patterns of calcification identified in a SPN by CT are highly specific for a benign diagnosis. However, the overall specificity of CT is poor because most lesions have indeterminate features and require invasive procedures for diagnosis¹⁰ (III-O).**
- **An algorithm using low-dose helical CT followed by other investigations has recently been shown to be accurate in distinguishing benign from malignant SPNs¹¹. This is currently under further evaluation (II-O).**
- **Positron emission tomography (PET) has been shown in multiple studies to distinguish between malignant and benign SPNs with a sensitivity of 83–92% and specificity of about 90%^{12,13}. The overall cost-effectiveness of PET in relation to management of lung cancer has yet to be determined (refer to Chapter 10 and MSAC Assessment Report March 2000 <http://www.health.gov.au/haf/msac>).**

When the considerations above are combined with appropriate use of relatively non-invasive diagnostic procedures (see below), the need for surgical biopsy or excision of an undiagnosed SPN is low.

SPUTUM CYTOLOGY

Although cough is present in 50% of lung cancer patients at the time of diagnosis¹⁴, sputum cytology is frequently negative because of lack of sputum, the peripheral position of the lesion or because of false negatives.

The sensitivity of sputum cytology increases with the number of specimens obtained: from about 50% with a single specimen up to almost 90% with three or more specimens¹⁵. It is highest with centrally placed squamous cell carcinomas and lowest with both peripheral tumours and centrally placed small cell carcinomas, because most of the tumour is below the mucosa. The use of induced ultrasonic nebulised sputum¹⁶ and optimal processing¹⁷ also increases the sensitivity of sputum cytology for the detection of lung cancer.

The specificity of positive sputum cytology is high (97.9%)¹⁸ and it is a non-invasive, readily available and inexpensive test.

Guidelines - Lung Cancer - Sputum Cytology	Level of Evidence	Refs
Sputum cytology is recommended to help establish a positive diagnosis of lung cancer in individuals with a central pulmonary mass.	III-(O)	16,17

FINE NEEDLE ASPIRATION AND FIBREOPTIC BRONCHOSCOPY

Percutaneous fine needle aspiration of a peripheral lung lesion under radiographic guidance is a relatively non-invasive diagnostic procedure with a sensitivity for detecting lung cancer of over 85%^{19,20}. For SPNs the negative predictive value of FNA has been reported as ranging from 52–84%^{21,22}. Sampling error is a problem and many experts would not rely on the result of a negative FNA alone to manage a SPN. The main risk is pneumothorax in individuals with bullous lung disease. This becomes clinically important if the pneumothorax is large or if the patient has a limited respiratory reserve. The diagnostic yield of transbronchial biopsies for peripheral nodules and lung masses is 30–50%, and less for lesions smaller than 2cm^{23,24,25}. The addition of bronchoalveolar lavage, brushings and bronchoscopic aspiration can increase the yield to about 75%.

Lung cancer often develops in the **central airways** (especially the squamous and small cell types), usually as an endobronchial lesion. Bronchoscopy with washings, brushings and biopsies of an endobronchial lesion have a diagnostic yield (diagnostic accuracy) of close to 100%²⁶. Less commonly, a centrally located cancer has peribronchial and submucosal involvement causing extrinsic bronchial compression. Shure reported that bronchial biopsies have a lower yield in this setting (55%) whereas that of bronchoscopic needle aspiration was 71% and reached 91% with biopsies, needle aspiration, washings and brushings^{27,28}. Furthermore, bronchoscopy also gives staging information about central lesions.

Mediastinal and **peribronchial** masses can be sampled using a Wang needle with a diagnostic accuracy of 25–40%^{29,30}. Fine needle aspiration can also be used to establish the diagnosis of lung cancer in patients presenting with accessible metastatic lesions. Endobronchial ultrasound is a new technique that is being evaluated in lung cancer and may increase the diagnostic utility of the Wang needle biopsy technique.

Guidelines – Lung Cancer – Bronchoscopy and FNA	Level of Evidence	Refs
Fibreoptic bronchoscopy is a procedure that has a high diagnostic yield (accuracy) in lung cancer.	III-(O)	26,30
In the diagnostic approach to suspected endobronchial lung tumours, bronchoscopy is usually the appropriate initial investigation for endobronchial evaluation and pathological confirmation.	IV-(O)	28
Fine needle aspiration is an appropriate initial investigation option for the pathological diagnosis of peripheral lung lesions in the absence of contraindications.	IV-(O)	19,20

FLUORO-DEOXY GLUCOSE (FDG) PET SCAN

This non-invasive imaging technique has been found to be very accurate in differentiating benign from malignant pulmonary lesions where the lesion is of at least 1cm in size^{13,31,32}. A recent meta-analysis has suggested a sensitivity of 97% and a specificity of 78%³³. It was suggested that PET may be more accurate than FNA biopsy, with an accuracy of 94% compared to 86% respectively. It may also prove to be cost-effective^{34,35}.

PET has been useful in the diagnosis of lung masses where a tissue diagnosis is not possible. Its high negative predictive value for malignancy suggests that PET-negative lesions can be safely observed^{31,32}. False negative studies are rare, but have been reported in bronchioloalveolar carcinoma and certain low-grade adenocarcinoma. False positive results are not uncommon and have been reported in granulomatous disease such as sarcoidosis, tuberculosis and histoplasmosis³⁶. This is an important consideration when PET is used to select individuals for curative surgery (see below).

Guideline – Lung Cancer – PET Scanning in Diagnosis	Level of Evidence	Refs
PET scanning is accurate in differentiating benign from malignant pulmonary lesions. It is highly predictive for diagnosis of lung masses when a tissue diagnosis is not readily available.	I-(O)	31,32,33

3.3 STAGING LUNG CANCER

Accurate histological diagnosis should precede staging procedures. The pathological findings are best reported in a synoptic manner, as seen in Appendix 7.

NON-SMALL CELL LUNG CANCER

The aim of staging NSCLC is to accurately identify the group of patients who will have a survival benefit from surgical resection or radical chemoradiation (Stage I to IIIA). Inherent in this approach is the assumption that the individual is medically fit for, and agrees to, the treatment. It should also be understood that clinical stage (cTNM) is less accurate than pathological stage (pTNM), and will therefore be associated with different outcomes. Staging NSCLC at the time of diagnosis according to the TNM system (revised 2002), guides management and predicts outcome. Information about staging is also of epidemiological importance, being used for health resource planning and research.

Determination of T stage requires measurement of tumour size and determination of the presence or absence of atelectasis, pleural effusion, ipsilateral lung nodule(s), or involvement of central airways, mediastinal structures, the pleura, the chest wall, the diaphragm or a vertebral body. Determination of N stage involves identification of bronchial, hilar, mediastinal and extra-pulmonary lymphadenopathy.

In a few situations, simple radiology may be sufficient to define the T and N stages for practical purposes, for example, an obvious pleural effusion, direct chest wall invasion with bone erosion or gross hilar and mediastinal lymph node enlargement. However, in the large majority of cases, a chest x-ray does not define the T or N status accurately enough to guide management. In particular, a significant number of T1N0 and T2N0 lesions on chest x-ray staging are up-staged when reassessed with other staging techniques.

TNM STAGING

T staging

CT has been the conventional imaging modality in delineating the size and local extent of the primary cancer^{37,38}. In the assessment of chest wall invasion, the overall accuracy of CT has been reported to be 39–86%^{39,40,41}. Magnetic resonance imaging (MRI) has a similar reported accuracy but has been found to be more superior in the assessment of local invasion including brachial plexus involvement in superior sulcus tumour and in cases where the CT findings are equivocal. This is a result of MRI's superior soft tissue contrast resolution and multi-planar capabilities^{41,42,43,44}.

CT and MRI have similar reported accuracies in the assessment of mediastinal involvement, in the range of 50–90%, although MRI has been shown to be slightly better due to superior soft tissue contrast between tumour and fat and blood vessels^{45,46,47}.

FDG PET is not generally the modality of choice in the assessment of local extent and invasion due to its inferior resolution compared to CT/MRI. FDG PET has, however, been found to be useful in differentiating tumour from adjacent consolidated or collapsed lung, which may improve staging accuracy and treatment planning⁴⁸.

N staging

CT is the most widely used modality in the evaluation of hilar and mediastinal nodal disease using the size criteria in which a short axis more than 1cm is considered pathological⁴⁹. This is a non-specific criterion. Optimal scanning techniques including adequate contrast enhancement and thin sections of the hilar regions have significant impact on its diagnostic accuracy. As a consequence the sensitivity and specificity of CT N staging are approximately 60–65% and 60–70% respectively^{41,50,51,52}. Similar diagnostic accuracy has been reported with MRI⁴⁵.

Because CT assessment incorrectly over-stages or under-stages T and N status in up to 40% of cases⁵³ some form of surgical sampling is required to confirm the CT results⁵⁴. The value of mediastinoscopy as a staging procedure is widely accepted⁵⁵, however it is often limited by the accessibility of lymph nodes and is prone to sampling errors. Thus, in two studies a third of the negative mediastinoscopies were found to have disease at thoracotomy^{56,57}. Anterior mediastinotomy allows access to some nodes that cannot be sampled by mediastinoscopy.

Guideline – Staging Non-small Cell Lung Cancer	Level of Evidence	Refs
Patients with mediastinal nodes larger than 1cm in transverse diameter on CT who otherwise have resectable lung disease should undergo further staging evaluation.	I-(O)	51,54

PET staging of N status has an accuracy of around 90% (81–99% reported), sensitivity of 80–100% and specificity of 90–99%^{58,59,60}. A mean sensitivity of 79% and specificity of 91% for PET, and 60% and 77% respectively for CT, were reported in a meta-analysis⁵¹. FDG PET has also been shown to separate N2 and N3 disease reliably^{54,52,61}.

The high negative predictive value of PET in mediastinal staging allows patients with a negative scan to proceed to thoracotomy without invasive mediastinal staging⁶². False positive results have been reported in granulomatous disease and other inflammatory conditions, and surgical sampling of nodes may be required before denying curative treatment. Overall, FDG PET has been found to modify staging and change the management plan in 30–40% of patients^{61,56,54}.

Guideline – PET Scanning in Staging Non-small Cell Lung Cancer	Level of Evidence	Refs
PET has been found to be more accurate than CT in mediastinal nodal staging for non-small cell lung cancer. A negative PET is highly specific, but positive PET nodes are not always malignant and histological confirmation may be required before advancing to definitive management.	I-(O)	51,58,59

M staging

Metastatic NSCLC causes problems for staging because it is common, involves many different sites without any predictable patterns and is often asymptomatic. The common metastatic sites are liver, adrenals, brain and bone, however, many other regions can be involved. About 25% of patients are found to have metastases at presentation⁶³ and many of these do not have extensive local disease^{64,65}. There is a correlation between T and N stage and the presence of metastases with squamous cell carcinoma but not with large cell or adenocarcinoma⁶⁵.

If the clinical assessment for metastases is positive at presentation, 50% of patients will have metastases. However, many patients found to have metastases on routine screening are asymptomatic⁶⁵. Also postmortem studies of patients who died in the peri-operative period following curative surgery⁶⁶, and PET studies of individuals staged by conventional methods as M0, have shown occult metastases in about 20%^{67,68}.

In spite of the risk of occult metastases, there is no good evidence to recommend routine imaging of extrathoracic sites in all cases of NSCLC in the absence of suspicious clinical or laboratory findings^{40,41,69,70}.

In Australian practice, imaging of the upper abdomen is routinely included in CT scanning of the thorax performed for T and N assessment. Isolated liver metastases are uncommon⁶³ and the impact of CT of the liver on M staging is low. Adrenal lesions are frequently seen, but two thirds are adenomas⁷¹. Chemical shift MRI imaging is reliable

in differentiating adenomas from adrenal metastases when CT findings are equivocal⁷². Other alternatives include CT densitometry using non-enhanced CT attenuation of the lesions, washout of CT contrast enhancement⁷³ and PET scans. However, biopsy confirmation is generally required before altering management.

Bone metastases are found at presentation in 9–15% of patients. Most of these are apparent clinically or cause an elevated serum calcium or alkaline phosphatase. A plain radiograph, radionuclide bonescan or MRI are useful modalities to investigate suspected bony metastases. Because the incidence of occult bony metastases is less than 4%^{64,70}, routine bone scans are not recommended.

Isolated cerebral metastases are rare and asymptomatic disease is reported in only 2.7–9.6% of patients, usually with large cell carcinoma or adenocarcinoma^{74,75}. The value of routine brain imaging in asymptomatic NSCLC (all types) is not established, although it is often done for large cell carcinoma and adenocarcinomas. Both CT and MRI are used to detect cerebral metastases, though MRI is the more sensitive modality⁶⁴.

PET is more accurate in the detection of metastatic disease in adrenal glands and the skeleton compared to CT and radionuclide bone scan^{76,77,78}. Occult extrathoracic metastases were detected in up to 24% of patients by whole body FDG PET^{67,68,79}. Overall, staging by PET has been shown to be more accurate than conventional imaging and this can impact on clinical management in up to two thirds of patients and may be cost-effective in clinical practice^{61,68,80,81}. PET staging has been found to be a powerful predictor of survival and translates to more superior prognostic stratification compared to conventional staging methods^{56,68,82}.

In summary, M staging of NSCLC is difficult because there are no clearly proven pathways using conventional tests, and PET, which is clearly superior for detecting (non-cerebral) metastases, is not universally available. The following guidelines are recommended:

Guidelines – M Staging of Non-small Cell Lung Cancer	Level of Evidence	Refs
If clinical assessment for metastases is abnormal, then further investigations are indicated, as metastases will be confirmed in 50% of such cases.	I-(O)	65
Routine bone scanning in non-small cell lung cancer is of little clinical value if there are no abnormal clinical or biochemical features.	III-(O)	64,70
The role of routine brain imaging in non-small cell lung cancer asymptomatic patients is unclear; but the detection rate is low.	III-(O)	74,75

Guidelines – M Staging of Non-small Cell Lung Cancer <i>(continued)</i>	Level of Evidence	Refs
PET is more accurate in overall M staging than conventional staging methods.	II-(O)	76,77,78

SMALL CELL LUNG CANCER (SCLC)

Small cell lung cancer (SCLC) comprises 15–25% of all lung cancers. It is distinguished from NSCLC by a rapid tumour doubling time and high growth fraction. Small cell lung cancer forms in the central airways in 80–90% of cases. At presentation up to 70% have already metastasised; most commonly to bone, liver, brain, bone marrow, retroperitoneal lymph nodes, soft tissue and adrenals.

STAGING SYSTEM

Accurate staging is important in SCLC because it guides treatment and helps to predict outcomes. However, the TNM staging system is not as useful for SCLC as with NSCLC because at presentation more than 90% of SCLC have either locally invasive mediastinal disease or metastases. Surgical management is rarely an option and therefore accurate intrathoracic staging is usually not required. In the few patients who do present with very localised SCLC and undergo surgical resection, the TNM staging system is prognostically important^{83,84}.

The staging system used for the majority of SCLC divides them into limited disease and extensive disease at presentation (see Appendix 2). Limited disease essentially consists of tumour involving a single hemithorax and its regional lymph nodes, however, there are several controversial issues (see Appendix 2). Whilst all patients with SCLC are treated with combination chemotherapy, limited disease stage defines a group who have a better prognosis and who benefit from the routine addition of thoracic radiotherapy.

STAGING PROCEDURES FOR SCLC

Until recently full anatomical staging using several imaging modalities and bone marrow biopsy has been standard practice in Australia and the USA. In contrast, European groups have used clinical and blood markers along with limited imaging techniques to group patients into limited disease or extensive disease stages and to predict prognosis. There is now good evidence that the latter approach is at least as good at determining treatment groups and predicting outcome and it is substantially cheaper, less invasive and simpler.

This more limited and targeted approach has now been advocated for routine use by a number of North American expert panels^{10,85,86}. It essentially consists of information from the clinical examination, a number of blood markers and a step-wise imaging approach to establish extensive disease or limited disease stage. Once a site of extensive disease is established further imaging is not required⁸⁷.

Guideline – Staging – Small Cell Lung Cancer	Level of Evidence	Refs
Once a metastatic site is identified, further anatomical staging at asymptomatic sites does not alter standard treatment or prediction of outcome but it does increase costs.	II	87

3.4 PROGNOSTIC FACTORS

The literature related to prognostic factors in both NSCLC and SCLC is extensive, and a thorough review is beyond the scope of this document. The reader is referred to the UICC publication on prognostic factors⁸⁸ and a consensus statement⁸⁹ for a more comprehensive treatment of the subject and relevant bibliography.

NON-SMALL CELL LUNG CANCER

A consensus group of the International Association for the Study of Lung Cancer, after reviewing the literature, agreed that TNM stage; performance status; and weight loss are independent prognostic factors in patients with NSCLC. The group also listed a number of possible factors, these included sex; serum LDH and albumin; haemoglobin, white cell count and platelets; and age. Histology was thought to be a possible factor in patients with early stage squamous cell carcinoma, inasmuch as the recurrence rate for patients with T1N0 disease has been reported to be lower than that of patients with adenocarcinoma when both are treated by surgical resection⁹⁰. Although certain biologic and molecular markers show considerable promise as prognostic factors, it is not yet clear that any of these provides consistent additional information over and above what is available from stage, performance status and weight loss^{91,92}.

The UICC’s publication on prognostic factors divides them into three categories: disease related, patient related and environment related⁹³. It further recognises that there may be differences in the prognostic significance of some factors depending on disease extent and type of treatment⁸⁸.

For NSCLC, essential prognostic factors are:

- tumour related
- stage
- hypercalcaemia
- superior vena caval obstruction
- patient related
- performance status
- weight loss
- environment related
- resection margin (for patients managed surgically)
- chemoradiotherapy for selected Stage III
- chemotherapy for selected Stage IV.

Two studies have suggested that experience with administering treatment may also be an important environmental prognostic factor. The survival of patients was superior both for surgery⁹⁴ and chemoradiotherapy⁹⁵ in institutions with greater experience.

Guideline – Non-small Cell Lung Cancer – Prognosis	Level of Evidence	Refs
TNM stage, performance status and weight loss are independent prognostic factors in patients with non-small cell lung cancer, and should be documented at diagnosis in all patients.	IV	88

SMALL CELL LUNG CANCER

As with NSCLC, stage is an essential prognostic factor in SCLC, but is usually simplified as either limited or extensive. The definitions of these staging terms are not always consistent between institutions, as the distinction limited disease – defined as that which can be encompassed within an ‘acceptable’ radiotherapy field – is dependent on subjective assessment by a radiation oncologist. There is a case to be made for a more objective staging system, perhaps a return to TNM, to better refine prognostic categories and guide treatment. Additional disease related factors include serum LDH and the presence of brain metastases⁸⁸. Performance status is an essential host related factor, with age, sex and weight loss as additional factors^{88,96}.

Guideline – Small Cell Lung Cancer – Prognosis	Level of Evidence	Refs
In patients with small cell lung cancer, stage (limited versus extensive) and performance status are essential prognostic factors, and should be documented at diagnosis in every case.	IV	88

3.5 FOLLOW-UP

Follow-up of cancer patients, especially those who have been treated with curative intent, is a traditional practice often performed regardless of the efficacy of available salvage therapies. Assessment of response to treatment can provide prognostic information⁹⁷ and is important to the patient who may wish to plan for the future. Benefits attributed to ongoing follow-up of patients who have been treated for lung cancer include: recognition and treatment of toxicities; identification and treatment of second primary lung cancers or metastatic disease; and periodic reassurance for the patient if recurrent disease is not found. Accurate follow-up information is useful for clinical audit and research. However, there are costs involved, particularly if imaging or procedures such as bronchoscopy form part of the process (refer to p 200). A systematic review of follow-up of lung cancer patients who had been treated with curative intent could find no evidence of a patient benefit from the use of advanced imaging (CT or PET) or serum levels of tumour markers⁹⁸. Further, the authors found no evidence that any particular strategy led to a survival advantage. They recommended that patients be followed for three to six-monthly after curative therapy in order to detect and manage complications, and thereafter at six monthly intervals for two years and then annually. A reasonable assessment at each visit would consist of a history, physical examination and chest x-ray.

Quality of life and patient satisfaction were assessed in a UK trial in which patients who had completed their initial anticancer treatment were randomised to follow-up by clinical nurse specialists in lung cancer or to routine two to three-monthly routine medical outpatient appointments⁹⁹. Patients randomised to nurse led follow-up rated their dyspnoea significantly less severe at three months compared with those receiving conventional medical follow up; they were less likely to have chest radiographs, and more likely to have radiotherapy. Patient satisfaction was consistently better on the nurse led follow-up arm. There was no difference in survival between the two arms. The role of the specialist lung cancer nurse in follow-up of lung cancer patients would seem to be worthy of research in the Australian setting.

Guideline – Follow-up	Level of Evidence	Refs
<p>There is insufficient evidence to recommend any particular schedule of follow-up of patients after treatment for lung cancer. After the period of risk for treatment-related complications has elapsed, six monthly clinical assessments with a chest x-ray is reasonable. There is no evidence that higher levels of imaging (CT or PET), tumour markers or bronchoscopy in asymptomatic patients have any influence on outcome and their routine use in follow-up is not recommended.</p>	IV	98

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