Clinical Practice Guidelines
FOR THE PREVENTION, DIAGNOSIS AND MANAGEMENT OF LUNG CANCER

APPROVED BY

Australian Government
National Health and Medical Research Council
Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Lung Cancer
These guidelines were approved by the National Health and Medical Research Council at its 152nd Session on 18 March 2004, under section 14A of the National Health and Medical Research Council Act 1992. Approval for the guidelines by NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every five years. Readers should check with The Cancer Council Australia for any reviews or updates of these guidelines.

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician’s judgement and the patient’s preference in each individual case.

The guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of compilation (September 2002).

Conflict of interest

The development of these clinical practice guidelines has been by a non-remunerated working party of the Australian Cancer Network with further support from The Cancer Council Australia, the Clinical Oncological Society of Australia and a grant in support from the Department of Health and Ageing to the National Cancer Control Initiative for editing and review services.

Some members of the working party have received sponsorship to attend scientific meetings; been supported in the conducting of clinical trials; or been involved in an advisory capacity by pharmaceutical houses.

These guidelines can be downloaded from the National Health and Medical Research Council website: www.nhmrc.gov.au/publications. Copies of the document can be ordered through the Australian Cancer Network on (02) 9036 3120 or email acn@cancer.org.au.
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FOREWORD

In 1993, the National Health and Medical Research Council (NHMRC) established a working party to develop clinical practice guidelines for the management of early breast cancer. According to Professor Richard Smallwood, the then chair of the NHMRC, “the objective of the guidelines is not only to assist practitioners to make decisions about appropriate health care for specific clinical circumstances, but also to assist consumers by providing them with comprehensive information about choices available in their treatment.” The development of the guidelines was based on two key principles: it had to be a multidisciplinary process and the guidelines were to be based on the best available evidence.

The early breast cancer guidelines were published in 1995 in two editions; one for the professional carers of women with breast cancer, and one for consumers. After endorsement by the NHMRC they were published in conjunction with the National Breast Cancer Centre.

Following the success and wide acceptance of the early breast cancer guidelines, the newly established Australian Cancer Network proceeded with the development of guidelines for other common cancers. To assist in this process, the NHMRC has published A guide to the development, implementation and evaluation of clinical practice guidelines1. To date clinical guidelines for melanoma, familial and colorectal cancer have been published and are widely used. At the time of writing, guidelines for the management of non-melanoma skin, prostate and epithelial ovarian cancer were under development, and it seemed logical that lung cancer, which is responsible for 22.8% of male and 14.8% of female cancer deaths in Australia2, more than any other, should also be included in the program.

That there was a need for management guidelines was evident from two recent Australian surveys of lung cancer management. The first of these, based on Victorian data from 1993, and published in 2000, revealed that 16% of patients with small cell lung cancer, and 21% with non-small cell lung cancer received no treatment at all3. In the second survey of Australian respiratory physicians and oncologists conducted in 1996, a wide variety of treatment recommendations were made for a single hypothetical case scenario4. For a patient with a T2N2M0 adenocarcinoma of the left main bronchus with a positive subcarinal node, there were similar levels of support for no fewer than six different treatment strategies. Such a variety of approaches to the same problem might be due to an absence of good evidence supporting any one approach, or it might be that busy practitioners do not have the time to carefully evaluate and weigh the existing evidence.

It might be asked ‘What difference are guidelines likely to make in a disease with an almost uniformly poor prognosis?’ Some sobering comparative international survival data suggest that differences in philosophy and management may be important. Recently reported five-year survival for lung cancer in the UK was only 6%, compared with 11% for New South Wales and 14% for US whites5. While some of these differences
may be due to the distribution of prognostic factors in the various patient populations, it is unlikely that there are major differences in the natural history of the disease from country to country, and it therefore seems probable that the management policies and practices were also contributory.

Survival is not the only measure of success in patients with lung cancer. Symptom palliation and quality of life may be more important considerations for the majority of patients who have incurable disease. It is noteworthy that in the Victorian survey, ‘good’ symptom control was achieved in only 55% of those patients treated with palliative intent².

A Working Party to develop guidelines for the management of lung cancer was assembled with the assistance of Emeritus Professor Tom Reeve from the Australian Cancer Network, and met for the first time in Melbourne in April 2000. The members of the working party were selected because of their area of expertise, as well as ensuring wide geographic representation to reflect the national nature of the project. All medical members, who were drawn from the clinical interest groups involved in the prevention, diagnosis and treatment of lung cancer, had the endorsement of the college with which they are affiliated. In addition to the medical members, the working party also had nursing and consumer representatives.

Using the NHMRC document¹ as their guide, the members formed smaller multidisciplinary groups to examine the best available evidence in order to make recommendations under the following headings:

- prevention and screening
- initial and pretreatment assessment
- supportive care
- non-small cell lung cancer (locoregional)
- non-small cell lung cancer (metastatic/ recurrent)
- small cell lung cancer.

The Working Party decided that the management of pleural mesothelioma would not be part of its brief.

The evidence would be researched and assigned to a level according the following scale:

I  Evidence obtained from a systematic review of all relevant randomised controlled trials.

II  Evidence obtained from at least one properly designed randomised controlled trial.

III.1 Evidence obtained from well designed pseudo-randomised controlled trials (alternate allocation or some other method).

III.2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised [cohort studies], case-control studies, or interrupted time series with a control group.
III.3 Evidence obtained from comparative studies with historical control, two or more single arm studies or interrupted time series without a parallel control group.

IV Evidence from case series, either post-test or pre-test and post-test.

For diagnostic tests, for which randomised trials may not be appropriate, the scale of evidence used is that recommended by the Oxford Centre for Evidence Based Medicine\textsuperscript{6}. This scale has been included as Appendix 7.

For some clinical scenarios, high-level evidence supporting one intervention over another may not be available; where this is the case, the guidelines say so, and make recommendations about the further research that is required.

In considering the evidence, the Working Party has taken account of an intervention’s effectiveness, rather than its cost.

A preliminary set of guidelines, based on evidence obtained from searches of electronic databases and with the assistance of the Cochrane Collaboration, was presented to a workshop held in Brisbane in association with the Annual Scientific Meeting of the Thoracic Society of Australia and New Zealand in March 2001. The guidelines were then further refined after the Working Party’s meeting in June 2001, and have undergone a significant editing process since that time.

The process has been specifically designed so as not to exclude contributions from individuals or groups who have additional evidence that may have escaped the notice of the working party members. The draft guidelines were advertised for public review and 23 submissions were received. An executive committee under the chair of Professor Robert Burton reviewed the submissions and appropriate incorporation or modifications made in the guidelines where necessary. Each question raised has been considered. The submissions were collated in exemplary fashion by Dr Karen Pedersen of the National Cancer Control Initiative (NCCI). The intention is to make the best evidence widely available to inform the decisions of health care professionals and consumers; the guidelines are not prescriptive. We have tried to keep the document succinct so that it is easy to use in everyday practice. It is not intended to be a comprehensive textbook of lung cancer. For those who wish to examine the evidence in more detail, references have been provided alongside every guideline.

During the review process, it was pointed out that some of the guidelines were based on studies which were unblinded to both the researcher and the reviewer, yet the evidence was classified as level I. The reality is that for many treatments in oncology, their method of administration and associated toxicities make double blind studies impractical. Further, the use of hard endpoints such as survival in many of the studies diminishes the risk of observer bias in interpreting the outcome.

A number of the reviewers felt that it was not enough to state in the guideline boxes that there were differences between treatments, but asked if it was possible to include some standard measure of the magnitude of any differences, for example increase
in median survival in months. However, the differences in outcome can be expressed in so many ways – median, one-year, five-year survival; hazard ratios and per cent reduction in risk of death; palliation, toxicity and quality of life outcomes and so on – that a standard method of quantifying differences was not thought appropriate.

The chapters dealing with the treatment of lung cancer are subdivided into sections according to therapeutic modality, rather than disease stage. We recognise that in the modern era of multidisciplinary care, this method of presenting the evidence may limit its practical application. We have therefore included tables at the beginning of Chapters 5 and 6 in which the recommended management of lung cancer is set out by stage to reflect the clinical situations which confront the practicing clinician.

Publication of the guidelines does not complete the process. Unless there is evidence of the implementation of the guidelines in practice, then the whole exercise will have achieved nothing. A meeting is to be held prior to the Annual Scientific Meeting of the Thoracic Society of Australia and New Zealand in April 2003 under the auspices of NCCI. This meeting should provide a powerful springboard for the dissemination and implementation. Once the guidelines have been disseminated, they will need to be piloted in hospitals and clinics to test their applicability and relevance. Next, they will need to be evaluated, in particular whether their implementation has had any effect on health outcomes. Finally, they will need to be revised within five years to ensure they reflect contemporary knowledge.

The Working Party noted that the following topics should be considered as research priorities:

1. Screening of high-risk populations using new imaging technologies.
2. The role of surgery in locally advanced non-small cell lung cancer.
4. Role of multidisciplinary care in lung cancer.
5. Role of clinical lung cancer nurse specialist.
6. Barriers to patient access to optimal care.
7. Improved palliation of dyspnoea.
8. Developing appropriate follow-up criteria and strategies.

The Working Party hopes that health practitioners and consumers find the Guidelines for the prevention, diagnosis and management of lung cancer a useful resource in the management of this difficult disease. We welcome feedback on any aspect of this publication.

**Associate Professor David Ball**

Chair, ACN Management of Lung Cancer Guidelines Working Party
References


EXECUTIVE SUMMARY

- Lung cancer causes a major burden to the health of Australians in terms of morbidity and mortality.

- The *Guidelines for the prevention, diagnosis and management of lung cancer* provide an evidence-based document produced by a multi-disciplinary working party to facilitate sound decision-making. The Guidelines are guidelines; they are not rules and are not prescriptive in any sense.

- Tobacco smoke and inhalation of environmental tobacco smoke, medical radiation in some specific subgroups and a history of previous lung disease are factors associated with an increased risk of lung cancer.

- Effective interventions through the medical profession, nursing and individual or group counselling can be helpful in assisting people not to start or to quit smoking. Personalised information is more effective than general information.

- Assessment of people with suspected pulmonary neoplasm is multi-factorial and should not rely on chest X-ray alone. Evaluation should aim to provide a defined diagnostic outcome and an appropriate therapeutic path.

- No defined pattern for screening for lung cancer has yet been established. Newer approaches eg. with or without spiral CT are being explored.

- Surgical resection of **non-small cell lung cancer** gives the best results of any form of treatment. Radiation and chemotherapy of patients with non-small cell lung cancer need to be carefully aligned to stage of disease and risks of surgery.

- **Small cell lung cancer** is rarely a surgical disease. Radiotherapy and chemotherapy both play significant roles in patient management and their application needs to be evaluated in relation to the patient's clinical status.

- Palliative care and psycho-oncology services provide significant assistance to clinicians, patients and their families. It is important that such assistance be sought in the management of patients with lung cancer.

- Palliative care may include a wide range of clinical services including surgery, radiotherapy, chemotherapy, physiotherapy, etc.

- The Guidelines have a valuable Appendix directing attention to asbestos and other environmental carcinogens. (Appendix 5)
## SUMMARY OF RECOMMENDATIONS AND GUIDELINES

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<td>Effective interventions include advice from doctors, structured interventions from nurses, and individual/group counselling.</td>
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<td>Generic self-help materials are no better than brief advice, but more effective than doing nothing.</td>
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<tr>
<td>Personalised materials are more effective than standard materials.</td>
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<td>All currently available forms of nicotine replacement therapy are effective.</td>
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<td>Bupropion and nortriptyline increase effectiveness as evidenced by quit rates.</td>
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<td>Personalised smoking cessation advice for inpatients together with at least one month of follow-up increases quit rates.</td>
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<td>Acupuncture, hypnotherapy, aversion therapy, immunotherapy and exercise have not been shown to effectively increase quit rates.</td>
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<td>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.</td>
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<td>Patients with mediastinal nodes larger than 1 cm in transverse diameter on CT who otherwise have resectable lung disease should undergo further staging evaluation.</td>
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<td>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.</td>
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<td>If clinical assessment for metastases is abnormal, then further investigations are indicated, as metastases will be confirmed in 50% of such cases.</td>
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<td>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.</td>
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<tr>
<td>Prognosis – SCLC</td>
<td>IV</td>
<td>88</td>
<td>60</td>
</tr>
<tr>
<td>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.</td>
<td></td>
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<tr>
<td>Follow-up</td>
<td>IV</td>
<td>98</td>
<td>61</td>
</tr>
<tr>
<td>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.</td>
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<tr>
<td>SECTION III: PATIENT SUPPORT AND DEFINITIVE TREATMENT</td>
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<td>Chapter 4 – Supporting the Patient During Diagnosis and Treatment</td>
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<td>Informing the Patient</td>
<td>III–3</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>Patients should be provided with adequate information, as this is associated with enhanced patient psychological wellbeing.</td>
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<tr>
<td>Clinicians should follow the NHMRC recommended guidelines on the breaking of bad news, providing information about treatments and the discussion of prognosis.</td>
<td>IV</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td><strong>Psychosocial Care in Lung Cancer</strong></td>
<td></td>
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</tr>
<tr>
<td>It is critical to recognise distress, anxiety and depressive disorders in patients with lung cancer as treatment with combined pharmacotherapy (antidepressants) and psychotherapy is efficacious.</td>
<td>I</td>
<td>2,26,27</td>
<td>73</td>
</tr>
<tr>
<td><strong>Quality of Life in Lung Cancer</strong></td>
<td></td>
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</tr>
<tr>
<td>The potential impact of treatment on quality of life in patients with lung cancer should be included in discussions of treatment alternatives.</td>
<td>II</td>
<td>18,30,31, 32,33,34</td>
<td>74</td>
</tr>
<tr>
<td><strong>Psychosocial and Supportive Services in Quality of Life in Cancer</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Psychological interventions and early referral to psycho-oncology and palliative care services improves quality of life in patients with cancer.</td>
<td>I</td>
<td>2,26,27</td>
<td>75</td>
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<td></td>
<td>II</td>
<td>38,39</td>
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<tr>
<td><strong>Chapter 5 – Non-Small Cell Lung Cancer (NSCLC)</strong></td>
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<tr>
<td><strong>Surgical Resection</strong></td>
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<tr>
<td>Surgical resection is recommended for early stage non-small cell lung cancer, as this gives the best results of any form of treatment.</td>
<td>II</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td><strong>Lobectomy</strong></td>
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<tr>
<td>Lobectomy is preferred to limited resection in patients with operable T1 N0 NSCLC.</td>
<td>II</td>
<td>16</td>
<td>86</td>
</tr>
<tr>
<td><strong>Regional Lymph Node Assessment</strong></td>
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<tr>
<td>Regional lymph node assessment should be performed with all lung resections for NSCLC. Radical mediastinal lymph node dissection whilst more accurately staging the patient provides no significant survival advantage over appropriate mediastinal lymph node sampling.</td>
<td>II</td>
<td>19,20,22</td>
<td>87</td>
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<tr>
<td>Radiotherapy</td>
<td>II</td>
<td>25</td>
<td>89</td>
</tr>
<tr>
<td>In patients with inoperable NSCLC and who have no evidence of distant metastases, radiotherapy is recommended to locoregional disease because it may be associated with a survival advantage compared with placebo.</td>
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<tr>
<td>Radiotherapy Dose</td>
<td>II</td>
<td>28,31</td>
<td>89</td>
</tr>
<tr>
<td>In patients with locoregional inoperable NSCLC and with good performance status, higher doses of radiotherapy are associated with better response and possibly survival. Doses in the vicinity of 60Gy in six weeks are recommended because they are safe and give the highest response rates.</td>
<td></td>
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<tr>
<td>Radiotherapy and Chemotherapy</td>
<td>I</td>
<td>35,36</td>
<td>90</td>
</tr>
<tr>
<td>The combination of cisplatin-based chemotherapy and radical radiotherapy in patients with good performance status is associated with a small but significant survival advantage compared with radiotherapy alone in NSCLC.</td>
<td></td>
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<tr>
<td>Timing of Radiotherapy and Cisplatin Therapy</td>
<td>II</td>
<td>42,43</td>
<td>91</td>
</tr>
<tr>
<td>Concomitant cisplatin and radiotherapy are associated with a better survival than if the two treatments are given sequentially.</td>
<td></td>
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</tr>
<tr>
<td>When to Avoid Radiotherapy</td>
<td>I</td>
<td>55</td>
<td>92</td>
</tr>
<tr>
<td>Postoperative radiotherapy in patients with completely resected Stage I or II NSCLC is not recommended because of its detrimental effect on survival.</td>
<td></td>
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<tr>
<td>Adjuvant Therapy</td>
<td>I</td>
<td>35</td>
<td>94</td>
</tr>
<tr>
<td>The administration of adjuvant platinum-based chemotherapy is not recommended following surgery because it has not been definitively shown to significantly improve survival.</td>
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<tr>
<td><strong>Neo-adjuvant Therapy</strong>&lt;br&gt;For Stage IIIA patients managed surgically, platinum-based combination chemotherapy should be given prior to surgery as it improves survival.&lt;br&gt;Neo-adjuvant chemotherapy may be beneficial in earlier stage disease, but the evidence is currently insufficient to support routine use (see Table 3–5).</td>
<td>II</td>
<td>51,52, 59,60</td>
<td>95</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong>&lt;br&gt;Chemotherapy is appropriate treatment for patients with advanced NSCLC who have good performance status (ECOG ≤ 2) and are otherwise medically fit as it has been shown to improve survival.</td>
<td>I</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>Chemotherapy can result in beneficial effects on symptoms and quality of life in patients with advanced NSCLC.</td>
<td>II</td>
<td>69,70</td>
<td>100</td>
</tr>
<tr>
<td><strong>Combination Chemotherapy</strong>&lt;br&gt;Combination chemotherapy is preferable to single agent therapy in patients with advanced NSCLC.</td>
<td>I</td>
<td>76</td>
<td>101</td>
</tr>
<tr>
<td>For patients where combination chemotherapy is contraindicated, single agent therapy with one of the ‘new’ agents (either a taxane, gemcitabine or vinorelbine) is appropriate.</td>
<td>II</td>
<td>83,84</td>
<td>101</td>
</tr>
<tr>
<td><strong>Choice of Chemotherapy Agents</strong>&lt;br&gt;At the present time, no one chemotherapy regimen can be recommended over another. Based on currently available trial results, various combinations of a platinum drug plus a ‘new’ agent are reasonable options for performance status 0 or 1 patients. The use of combinations of three or more drugs, and the use of non-platinum combinations require further investigation before incorporation into standard practice.</td>
<td>II</td>
<td>85,86, 87,88</td>
<td>104</td>
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<tr>
<td>Carboplatin can be used instead of cisplatin in combination chemotherapy.</td>
<td>II</td>
<td>92, 93, 94</td>
<td>104</td>
</tr>
<tr>
<td>Chemotherapy Doses and Cycles</td>
<td>II</td>
<td>85, 102, 103, 104</td>
<td>105</td>
</tr>
<tr>
<td>There is no indication to use greater than standard doses or dose intensity of chemotherapy in advanced NSCLC.</td>
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<tr>
<td>Continuing multi-agent platinum-based chemotherapy beyond three to four cycles does not provide additional survival benefit.</td>
<td>II</td>
<td>105, 106</td>
<td>105</td>
</tr>
<tr>
<td>Patients receiving chemotherapy for advanced NSCLC should be evaluated for effectiveness of treatment after two to three cycles. Treatment should be discontinued if no benefit is seen.</td>
<td>IV</td>
<td>106</td>
<td>105</td>
</tr>
<tr>
<td>Second Line Chemotherapy</td>
<td>II</td>
<td>108, 109</td>
<td>106</td>
</tr>
<tr>
<td>In selected good performance status patients, second-line chemotherapy with docetaxel may be considered.</td>
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<tr>
<td>Chapter 6 – Small Cell Lung Cancer</td>
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<td>117</td>
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<tr>
<td>Platinum as Optimal Chemotherapy</td>
<td>I</td>
<td>6, 7</td>
<td>123</td>
</tr>
<tr>
<td>Platinum containing regimens produce superior survival to that seen with other regimens.</td>
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</tr>
<tr>
<td>For patients with limited disease, when used in conjunction with thoracic irradiation, there is no evidence that any combination is superior to the doublet of cisplatin and etoposide.</td>
<td>I</td>
<td>12, 13</td>
<td>123</td>
</tr>
<tr>
<td>Cycles of Chemotherapy</td>
<td>II</td>
<td>2, 21, 22, 23</td>
<td>123</td>
</tr>
<tr>
<td>Four to six cycles of chemotherapy should be given.</td>
<td></td>
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<tr>
<td>First and Second Line Chemotherapy</td>
<td>II</td>
<td>33</td>
<td>125</td>
</tr>
<tr>
<td>Where a platinum agent and etoposide have been given first line, then appropriate second-line regimens include the combination of cyclophosphamide, Adriamycin and vincristine, or single agent topotecan. These regimens are of similar efficacy.</td>
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<tr>
<td>If first line chemotherapy has produced a response which has gone beyond eight months duration, it is reasonable to trial the first line drug again.</td>
<td>III–3</td>
<td>32</td>
<td>125</td>
</tr>
<tr>
<td><strong>Chemotherapy and Radiotherapy</strong></td>
<td></td>
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</tr>
<tr>
<td>In patients with limited stage small cell lung cancer, the addition of thoracic radiotherapy to standard combination chemotherapy improves overall survival and should be incorporated into a comprehensive treatment plan.</td>
<td>I</td>
<td>35,36,37</td>
<td>126</td>
</tr>
<tr>
<td>Thoracic radiotherapy should be offered early in relation to the course of chemotherapy rather than late. Evidence supports the administration of chemotherapy concurrent with radiotherapy over sequential chemotherapy-radiotherapy administration.</td>
<td>II</td>
<td>2,38,39, 40,41, 42,43</td>
<td>126</td>
</tr>
<tr>
<td>Accelerated radiotherapy is associated with a survival advantage compared with standard fractionation.</td>
<td>II</td>
<td>2</td>
<td>126</td>
</tr>
<tr>
<td><strong>Prophylactic Cranial Irradiation</strong></td>
<td></td>
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<tr>
<td>For patients who have achieved a complete response after induction therapy, prophylactic cranial irradiation is associated with a reduction in rate of brain metastases and prolongation of survival.</td>
<td>I</td>
<td>52</td>
<td>127</td>
</tr>
<tr>
<td><strong>SECTION IV: SYMPTOM CONTROL</strong></td>
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<tr>
<td><strong>Chapter 7 – Palliative Care</strong></td>
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<tr>
<td><strong>Specialist Palliative Care Services</strong></td>
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<tr>
<td>Specialist palliative care services should be used to improve outcomes in the care of patients with cancer (lung cancer included).</td>
<td>I</td>
<td>9</td>
<td>138</td>
</tr>
<tr>
<td><strong>Management of Dyspnoea</strong></td>
<td></td>
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<tr>
<td>Counselling, breathing retraining, relaxation, and teaching coping and adaptive strategies can improve dyspnoea and functional capacity in lung cancer patients.</td>
<td>II IV</td>
<td>42 64</td>
<td>145</td>
</tr>
</tbody>
</table>
Other non-pharmacological measures to be considered for dyspnoea include acupuncture as a complementary procedure.  

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</table>
| A therapeutic trial of morphine and/or benzodiazepines is recommended for dyspnoea in patients with advanced cancer. | II  
IV | 49  
65 | 145 |
| Nebulized morphine can improve dyspnoea in some terminally ill lung cancer patients. A supervised therapeutic trial may be worthwhile. | III–3  
IV | 53  
57,58 | 145 |
| Nebulized lignocaine has not proven to be better than nebulized saline in relief of breathlessness. | IV | 61 | 145 |

**Cough Suppression**

Oral opioids are recommended for suppression of non-productive cough in lung cancer.

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<tbody>
<tr>
<td>Inhaled sodium cromoglycate could be tried in cough from non-small cell lung cancer that is resistant to standard therapy.</td>
<td>II</td>
<td>69</td>
<td>146</td>
</tr>
<tr>
<td>Nebulised lignocaine can be useful as a cough suppressant - special precautions need to be taken (see text).</td>
<td>IV</td>
<td>51</td>
<td>146</td>
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</tbody>
</table>

**Pain Management**

Unrelieved or poorly controlled pain leads to increased anxiety about the future and general anxiety that interferes with daily living.

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<tr>
<td>Management of moderate to severe cancer pain should include the appropriate introduction and dose titration of opioids.</td>
<td>IV</td>
<td>73,75</td>
<td>150</td>
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</table>

**Neuropathic Pain Management**

Extrapolation from therapeutic approaches to neuropathic pain in other diseases indicates that antidepressants and anti-convulsants offer effective palliation.

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<td>I</td>
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<tr>
<td>Bowel Care</td>
<td>III–3</td>
<td>81</td>
<td>151</td>
</tr>
<tr>
<td>The best laxative for terminally ill patients using opioids is yet to be determined. Senna and lactulose have shown equal efficacy.</td>
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<tr>
<td>Management of Pleural Effusion</td>
<td>IV</td>
<td>87</td>
<td>152</td>
</tr>
<tr>
<td>Pleural effusion is best managed by talc insufflation following thoracoscopic exploration and complete drainage of fluid.</td>
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</tr>
<tr>
<td>Management of Pericardial Effusion</td>
<td>IV</td>
<td>89</td>
<td>153</td>
</tr>
<tr>
<td>Pericardiocentesis can be safely performed under echocardiographic control. The outcome is effective.</td>
<td></td>
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<tr>
<td>Chapter 8 – Palliative Radiation</td>
<td></td>
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</tr>
<tr>
<td>Radiotherapy in Palliation of Cancer</td>
<td>II</td>
<td>1,2,3</td>
<td>164</td>
</tr>
<tr>
<td>Radiotherapy is an effective modality for the management of certain symptoms caused by uncontrolled intrathoracic disease, and short courses of radiotherapy are as effective as more fractionated regimens.</td>
<td></td>
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<tr>
<td>There appears to be improved survival in patients with a good performance status receiving higher doses of palliative radiotherapy, compared to single or two fraction courses.</td>
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<tr>
<td>External beam radiotherapy appears to provide better palliation compared to endobronchial brachytherapy, but brachytherapy might be of benefit in patients with endobronchial obstructing lesions.</td>
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<tr>
<td>Superior Vena Cava Obstruction in Cancer</td>
<td>IV</td>
<td>9</td>
<td>165</td>
</tr>
<tr>
<td>A histological diagnosis is desirable before treatment of superior vena cava obstruction.</td>
<td></td>
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</tr>
<tr>
<td>Chemotherapy on its own is effective in superior vena cava obstruction due to small cell lung cancer.</td>
<td>II</td>
<td>10,11</td>
<td>165</td>
</tr>
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<td><strong>Management of Metastatic Spinal Cord Compression</strong></td>
<td>II III–3</td>
<td>15 16</td>
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<tr>
<td>Dexamethasone should be started on suspicion of spinal cord compression</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>and whilst awaiting assessment.</td>
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<tr>
<td>If spinal cord compression is suspected, whether</td>
<td>III–3</td>
<td>13,14</td>
<td>166</td>
</tr>
<tr>
<td>on symptomatic or clinical grounds the investigation of choice is MRI</td>
<td></td>
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<tr>
<td>scan.</td>
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<tr>
<td>Surgery followed by radiotherapy is the treatment of choice for</td>
<td>II</td>
<td>17</td>
<td>166</td>
</tr>
<tr>
<td>spinal cord compression.</td>
<td></td>
<td></td>
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<tr>
<td>When surgery is not considered appropriate, radiotherapy should</td>
<td>III–3</td>
<td>12,18,19</td>
<td>166</td>
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<tr>
<td>be started immediately. Radiotherapy is considered as effective as</td>
<td></td>
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<tr>
<td>surgery in achieving symptomatic relief.</td>
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<tr>
<td><strong>Radiotherapy in Management of Skeletal Metastases</strong></td>
<td>IV</td>
<td>20</td>
<td>168</td>
</tr>
<tr>
<td>Palliative radiotherapy remains the most effective single modality for</td>
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<tr>
<td>the treatment of local metastatic bone pain.</td>
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<tr>
<td>In the treatment of skeletal metastases trials have shown that 8Gy single</td>
<td>II</td>
<td>22,24,25,</td>
<td>168</td>
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<tr>
<td>fraction is as efficacious for pain relief as other schedules.</td>
<td></td>
<td>26,27,28</td>
<td></td>
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<tr>
<td>In patients who have widespread bony lesions consideration can be given</td>
<td>III–2</td>
<td>31</td>
<td>168</td>
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<td>to single fraction hemi-body radiation palliation.</td>
<td></td>
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<td><strong>Bisphosphonates in Management of Bone Metastases</strong></td>
<td>I</td>
<td>33,34,35</td>
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</tr>
<tr>
<td>Bisphosphonates improve pain in people with symptomatic bone metastases</td>
<td></td>
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<td>from lung cancer.</td>
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<tr>
<td><strong>Irradiation and Radiotherapy for Skeletal Metastases</strong></td>
<td>II</td>
<td>39,46, 47,</td>
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</tr>
<tr>
<td>Radiotherapy is effective palliation for brain metastases from lung</td>
<td></td>
<td>48</td>
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<td>cancer.</td>
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<tr>
<td>Resection of solitary cerebral metastases followed by radiotherapy</td>
<td>III–2 III–3</td>
<td>40,42</td>
<td>172</td>
</tr>
<tr>
<td>potentially results in increased local control and a longer disease-free</td>
<td></td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>survival than radiotherapy alone.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guideline</td>
<td>Level of Evidence</td>
<td>Refs</td>
<td>Page</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>------</td>
</tr>
<tr>
<td>Stereotactic radiosurgery may be a suitable alternative to resection.</td>
<td>III–3</td>
<td>43,44</td>
<td>172</td>
</tr>
<tr>
<td>Doses of whole brain radiotherapy ranging from 10Gy in a single fraction</td>
<td>II</td>
<td>39,48, 49,50</td>
<td>172</td>
</tr>
<tr>
<td>to 40Gy in 20 fractions have similar effectiveness in symptom palliation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and times to disease progression. Shorter courses, for example 20Gy in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>five fractions, are recommended because of patient convenience.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-irradiation for progressive brain metastases may be considered in</td>
<td>IV</td>
<td>52</td>
<td>172</td>
</tr>
<tr>
<td>selected patients without progressive disease at other sites.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chapter 9 – Alternative and complementary therapies</td>
<td></td>
<td></td>
<td>177</td>
</tr>
<tr>
<td>Educational and Psychosocial Care in Cancer</td>
<td>I</td>
<td>3</td>
<td>179</td>
</tr>
<tr>
<td>Educational and psychosocial care has been found to benefit adults with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cancer in relation to anxiety, depression, mood, nausea, vomiting, pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and knowledge.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aromatherapy and Anxiety in Radiotherapy</td>
<td>II</td>
<td>18</td>
<td>181</td>
</tr>
<tr>
<td>Aromatherapy has not been shown to reduce anxiety in patients with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cancer undergoing radiotherapy.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SECTION I
SETTING THE SCENE

1. EPIDEMIOLOGY

1.1 Lung cancer in Australia

1.2 Pathogenesis and classification

1.3 Aetiology
   Tobacco smoke
   Trends in smoking
   Environmental tobacco smoke
   Cannabis use and lung cancer
   Medical radiation
   Indoor radon
   Cooking fuels
   Previous lung disease
   Genetic susceptibility
   Asbestos and other environmental carcinogens

1.4 Survival
1.1 LUNG CANCER IN AUSTRALIA

Lung cancer is a serious health problem in Australia. It was the fifth most common cancer reported to Australian cancer registries in 1998, but the leading cause of death from cancer, responsible for 20.1% of cancer deaths\textsuperscript{1,2}. In the year 2000, lung cancer accounted for 22.8% of male and 14.8% of female cancer deaths and 5.3% of all deaths in Australia\textsuperscript{3}.

There were 7 795 new cases of lung cancer in Australia during 1998 and 6 893 deaths. About one in 28 Australians are likely to develop lung cancer during their lifetime and for those who died during 1998, there were an estimated 45 118 life-years lost as a result of premature death before reaching 75 years of age\textsuperscript{4}.

Over the period 1983–98, the incidence of lung cancer in males fell to 58 cases per 100 000 population whereas the incidence in females rose to 23 cases per 100 000 population. The mortality rate in males declined to 53 cases per 100 000 in 1998 but remained relatively stable in females at 19 cases per 100 000 population as shown in Figure 1–1\textsuperscript{1}. Prior to the mid-1980s the rates had been increasing in males for more than 50 years\textsuperscript{4,5}.

Figure 1–1  Trends in age-standardised incidence and mortality rates for cancer of the lung, Australia\textsuperscript{1}
The incidence and mortality rates increase with advancing age in both males and females. In 1998, the incidence rate peaked in the 75–79 year age group and the mortality rate peaked in the 80–84 year age group in both males and females in Australia. An important element of the current epidemiology of lung cancer in Australia is its migration to an older cohort. The fraction of new lung cancers that were seen above age 70 years increased from 39% in 1985 to more than 49% in 1995. This increase was from 40% to 50% in men and 37% to 48% in women. This becomes relevant as age and comorbidity affects the feasibility of some treatment options.

Lung cancer incidence and mortality vary between the states and territories (Figure 2–1). Both incidence and mortality age-standardised rates are markedly lower in males in the Australian Capital Territory (ACT) and higher in the Northern Territory. The rates in females are also notably higher in the Northern Territory. However, it should be noted that the numbers of cases in the Northern Territory and ACT are far lower than in the states, due to the relatively smaller populations in the territories.

The Australian lung cancer incidence and mortality rates are lower than rates in North America and Europe (Table 1–1). The Australian rates given in Table 1–1 are different to those above, because they have been standardised to the world standard population rather than the Australian population for purposes of comparison.

Figure 2–1  Average annual incidence and mortality rates from lung cancer, Australia 1994–1998

---

4  Clinical practice guidelines for the prevention, diagnosis and management of lung cancer
### Table 1–1  Incidence and mortality rates from lung cancer per 100 000 population, 1996, standardised to the world standard population

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence rate</th>
<th>Mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Australia</td>
<td>41.9</td>
<td>16.9</td>
</tr>
<tr>
<td>United States</td>
<td>58.5</td>
<td>33.9</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>46.0</td>
<td>21.5</td>
</tr>
<tr>
<td>European Union</td>
<td>52.3</td>
<td>11.2</td>
</tr>
</tbody>
</table>

### 1.2 PATHOGENESIS AND CLASSIFICATION

Lung cancer appears to arise in the bronchi in response to repetitive carcinogenic stimuli, inflammation and irritation. Disruption of cell development occurs in the mucosal lining and progresses to elevate or erode the basal membrane. The tumour then spreads throughout the lung and will eventually metastasise to the lymph nodes and other parts of the body.

There are four main histologic classifications of lung cancer. These are squamous cell carcinomas, adenocarcinomas, small cell carcinomas and large cell carcinoma. Because the behaviour and management of squamous cell carcinoma, adenocarcinoma and large cell carcinomas are very similar, they are often grouped together as non-small cell lung cancer (NSCLC) in contrast to small cell lung cancer (SCLC), which has a distinct natural history and management.

**Squamous cell** carcinoma is most commonly found in men and shows the strongest relationship with smoking. This tumour arises in the larger and more central bronchi and tends to spread locally. It metastasises later than other types, but grows rapidly at its site of origin.

**Adenocarcinoma** was previously known as the most common type of lung cancer in women and non-smokers, however, the incidence of adenocarcinoma has increased in the last two decades and it is now the most common histological subtype in both males and females. The reason for the increasing incidence of adenocarcinoma is not well understood, but may be related to changing patterns of smoking. Adenocarcinomas tend to be peripherally located, smaller and vary histologically from well-differentiated tumours to solid masses with occasional mucin-producing glands and cells.

**Small cell** carcinomas are highly malignant and have a distinctive cell type. They may be round and oval (oat cells) or have spindle-shaped or polygonal cells, and are probably derived from neuroendocrine cells of the epithelial lining of the bronchi. They have a...
strong relationship to cigarette smoking and are the most aggressive of all lung tumours, metastasising widely and virtually incurable by surgical means.

**Large cell** carcinomas are likely to be undifferentiated squamous cell and adenocarcinoma. They usually consist of large polygonal cells with vesicular nuclei\textsuperscript{10,11}.

### 1.3 AETIOLOGY

**TOBACCO SMOKE**

Smoking is the largest single cause of lung cancer, responsible for 90% of lung cancers in males and 65% of lung cancers in females in Australia, and continues to rise\textsuperscript{12}. Certain industrial exposures and atmospheric pollutants, including environmental tobacco smoke, also increase an individual’s risk of lung cancer (refer to Appendix 5, p 229).

The first case-control studies supporting a link between smoking and lung cancer incidence were published in the 1950s. Since that time, further evidence has accumulated to show the relationship of lung cancer incidence to the timing, duration, intensity and other characteristics of smoking.

Three of the largest cohort studies on current male smokers were those by Hammond, Doll et al and McLaughlin et al\textsuperscript{13,14,15}. These all found increased lung cancer death rates with increasing amounts smoked, such that those smoking 10 or more cigarettes per day had a relative risk of lung cancer of approximately 10. Similar results were found in females\textsuperscript{16,17}. Doll and Peto found that not only did the excess risk of lung cancer rise in proportion to the square of the number of cigarettes smoked per day, but to the fourth or fifth power of the duration of smoking\textsuperscript{18}. This effect has been replicated in other studies\textsuperscript{19,20}. Cigar and pipe smoking are also associated with increased risk of lung cancer, although the extent of the risk varies between studies. A relative risk of seven was found in the British Physicians Study compared with Swedish cohort studies, which found similar risks to those in cigarette smokers\textsuperscript{14,21}.

The relative risk of lung cancer declines with increased time since quitting, eventually approaching that of non-smokers\textsuperscript{13,14,15}.

The results of a 1995 meta-analysis\textsuperscript{22} of nine cohort studies and seven case-control studies on the effects of the relationship between cigarette smoking and lung cancer are shown in Table 2–1. This meta-analysis excluded studies published prior to 1980 and studies for which the majority of cases were diagnosed before 1975 in order to be representative of present day risk, as smoking habits and composition of cigarettes have changed substantially over time. Studies were also excluded if they did not separate the effects of former smoking from current smoking or never smoking, or there was no adjustment for age or control groups having smoking-related diseases.
Table 2–1  Pooled estimates of relative risks of lung cancer in former smokers and current smokers compared to never smokers

<table>
<thead>
<tr>
<th>Sex</th>
<th>Former smokers</th>
<th>Current smokers (cigarettes per day)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Any</td>
<td>1–14</td>
<td>15–24</td>
<td>25+</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6.75</td>
<td>13.00</td>
<td>6.49</td>
<td>8.56</td>
<td>15.10</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5.07</td>
<td>11.40</td>
<td>7.41</td>
<td>13.30</td>
<td>20.50</td>
<td></td>
</tr>
</tbody>
</table>

TRENDS IN SMOKING

Future trends in lung cancer incidence can be predicted from past trends in smoking because lung cancer due to smoking usually takes 20 years or more to develop. The smoking prevalence of adult Australians has declined from around 72% of males in 1945 to 26% in 2001. The percentage of females smoking rose from 26% in 1945 to 33% in 1976, and subsequently dropped to 21% in 2001. While there were significant declines in the prevalence of smoking among adults and secondary school students in the latter part of the twentieth century, the rate of decline has slowed since the 1990s. From these trends we would predict that the incidence of lung cancer in males will continue to fall and that the incidence of lung cancer in females will reach a peak before 2010.

There is a marked variation in smoking prevalence among population subgroups. The National Aboriginal and Torres Strait Islander Survey of 1994 found that among Indigenous Australians, 54% of males and 46% of females aged over 13 years reported that they smoked. The National Mental Health Survey found that 41.8% of Australians with a diagnosable mental health condition were current smokers. Furthermore, smoking prevalence has been shown to decrease with increased education and occupation status.

ENVIRONMENTAL TOBACCO SMOKE

Analysis of 39 published epidemiological studies of the risk of lung cancer in non-smokers who did and did not live with a smoker found an excess risk of lung cancer of 24% in female non-smokers who lived with a smoker. The meta-analysis included five cohort and 34 case-control studies and covered 4626 cases of lung cancer. The dose-response relationship showed that the risk of lung cancer in the non-smoker increased by 23% for every 10 cigarettes smoked per day by the smoker and by 11% for every 10 years of exposure (Table 3–1).
Table 3–1  Effect of environmental tobacco smoke on non-smokers

<table>
<thead>
<tr>
<th>Risk of lung cancer in female non-smokers living with a smoker</th>
<th>Excess risk</th>
<th>Relative risk (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of lung cancer for every 10 cigarettes smoked per day by cohabitant</td>
<td>23%</td>
<td>1.23 (1.14–1.32)</td>
</tr>
<tr>
<td>Risk of lung cancer for every 10 years of exposure resulting from living with a smoker</td>
<td>11%</td>
<td>1.11 (1.04–1.17)</td>
</tr>
</tbody>
</table>

The risk of lung cancer in non-smokers was also estimated by extrapolating from the risk in smokers, using urine or saliva concentrations of cotinine and nicotine. Cotinine and nicotine are tobacco specific and their concentrations in non-smokers exposed to environmental tobacco smoke are about 1% of those in smokers. Non-smokers exposed to environmental tobacco smoke therefore experience 1% of the excess risk of lung cancer seen in smokers. The relative risk of lung cancer in smokers compared to non-smokers was approximated to be 20, thus giving an excess risk of 19. Therefore, the excess risk of lung cancer in non-smokers exposed to environmental tobacco smoke compared with smokers was 0.19, that is 1% of 19.

**CANNABIS USE AND LUNG CANCER**

Cannabis is smoked in the same way as tobacco in many countries including Australia. Cannabis (marijuana) smoke contains many of the same carcinogens as tobacco smoke, with some differences in the levels of certain chemicals. It appears to be mutagenic in microbial assays and carcinogenic in some animal tests.

Cannabis use has been linked to the finding of molecular and morphological changes in bronchial epithelium, some of which can be found in at-risk or pre-neoplastic lesions of the airway. There are data linking cannabis use to aerodigestive cancers in the form of case reports. Otherwise, a large cohort study of nearly 65,000 people failed to show an overall excess of cancer comparing cannabis users and non-users at study entry (RR 0.9, 95% CI 0.7–1.2). However, the potential limitations of the study included the relatively young age at follow-up compared to the usual age range of lung cancer sufferers, a small number of heavy or long term users, and technical ascertainment issues. In contrast, a smaller case-control study reported that marijuana use was associated with an increased risk of head and neck cancer after adjusting for potential confounders including cigarette smoking.

Further studies are thus needed to more definitively assess the carcinogenic risk of cannabis smoke. Meanwhile, it is worth informing regular cannabis smokers, particularly those who also smoke tobacco, that they may have a higher risk of lung cancers based on current knowledge of the properties of cannabis and tobacco smoke.
MEDICAL RADIATION

The risk of lung cancer may be elevated as a result of medical exposure to radiation. A study of the effect of medical radiation on lifetime non-smokers found no elevated risk in males who had received radiotherapy, but an increased risk of 4.4 in females. This risk became non-significant when adjusted for history of reproductive cancer\textsuperscript{33}, although recent evidence suggests greater risks for medical radiation in smokers who have had breast cancer\textsuperscript{34}.

INDOOR RADON – SEE APPENDIX 5

COOKING FUELS – SEE APPENDIX 5

PREVIOUS LUNG DISEASE

The risk of lung cancer in people who have pre-existing lung disease has been studied using case-control studies. Lung diseases studied include asthma, chronic bronchitis, emphysema, pneumonia, pleurisy and tuberculosis. The results of some of these studies are outlined in Table 4–1. They provide evidence for increased risk of lung cancer following bronchitis and emphysema and possibly asthma and tuberculosis. However, most of the studies have been carried out in females and may not be generalisable to males. Nevertheless, early studies provided some evidence for increased risk of lung cancer mortality following asthma in males but not females\textsuperscript{35,36}. Despite adjustment for smoking, differing odds ratios have been observed between smokers and non-smokers. The effect of diet, environmental tobacco smoke, time between diagnosis of lung disease and lung cancer, and the lung cancer cell type also need to be more fully examined. For example, in the study of Mayne et al\textsuperscript{37}, the results were no longer supportive when further adjustment for dietary variables was added to the model. Furthermore, in the study of Wu et al\textsuperscript{38}, none of the odds ratios were significant when the model was adjusted for all previous lung disease, age, area, ethnicity and education.

GENETIC SUSCEPTIBILITY

Some genotypes are thought to be associated with an increased risk of lung cancer\textsuperscript{11}. It is hoped that further developments in molecular biology and epidemiology will greatly extend our knowledge in this respect.
ASBESTOS AND OTHER ENVIRONMENTAL CARCINOGENS

Several reviews published between 1991 and 2000 have supported the cumulative exposure model for lung cancer risk as a consequence of asbestos exposure\textsuperscript{39,40,41,42,43,44,45,46}, with no clearly delineated threshold\textsuperscript{40} and with no requirement for asbestosis or diffuse pleural fibrosis as a prerequisite for attribution of lung cancer to asbestos\textsuperscript{47}. Criteria for compensation of asbestos-related lung cancer and approaches to apportionment of the relative contributions of asbestos and cigarette smoke to lung cancer induction are discussed elsewhere\textsuperscript{39,46,47,48,49,50,51,52,53}.

A detailed review of 'Asbestos and other environmental carcinogens' can be found in Appendix 5.
Table 4-1  Age and smoking adjusted odds ratios (95% CI) for risk of lung cancer following previous lung disease in case-control studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Odds ratio adjustment</th>
<th>Asthma</th>
<th>Bronchitis</th>
<th>Emphysema</th>
<th>Pneumonia</th>
<th>Pleurisy</th>
<th>Tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brownson et al, 2000&lt;sup&gt;54&lt;/sup&gt;</td>
<td>Age, smoking</td>
<td>1.1</td>
<td>1.7</td>
<td>2.7</td>
<td>1.6</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.7–1.7)</td>
<td>(1.2–2.3)</td>
<td>(1.8–4.2)</td>
<td>(1.2–2.0)</td>
<td>(0.8–1.5)</td>
<td>(0.4–2.2)</td>
</tr>
<tr>
<td>Mayne et al, 1999&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Age, smoking</td>
<td>2.0</td>
<td>1.7</td>
<td>1.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.0–4.1)</td>
<td>(1.1–2.6)</td>
<td>(1.1–3.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alavanja et al, 1992&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Age, smoking</td>
<td>1.3</td>
<td>0.9</td>
<td>2.6</td>
<td>1.2</td>
<td>0.9</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.8–2.1)</td>
<td>(0.6–1.3)</td>
<td>(1.5–4.7)</td>
<td>(1.0–1.6)</td>
<td>(0.7–1.3)</td>
<td>(1.0–4.1)</td>
</tr>
<tr>
<td>Wu et al, 1995&lt;sup&gt;53&lt;/sup&gt;†</td>
<td>Age, area, ethnicity, education</td>
<td>1.7</td>
<td>1.6</td>
<td>2.6</td>
<td>1.4</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1.1–2.5)</td>
<td>(1.1–2.4)</td>
<td>(1.0–6.8)</td>
<td>(1.0–1.8)</td>
<td>(0.9–1.9)</td>
<td>(0.9–2.9)</td>
</tr>
<tr>
<td>Samet et al, 1985&lt;sup&gt;56&lt;/sup&gt;</td>
<td>Age, sex, ethnicity, smoking</td>
<td>–</td>
<td>1.7</td>
<td>1.6</td>
<td>–</td>
<td>–</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.2–2.5)</td>
<td>(1.1–2.4)</td>
<td></td>
<td></td>
<td>(0.7–2.9)</td>
</tr>
<tr>
<td>Wu et al, 1988&lt;sup&gt;57&lt;/sup&gt;‡</td>
<td>Age, smoking</td>
<td>1.0</td>
<td>1.2</td>
<td>1.9</td>
<td>1.4</td>
<td>1.4</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.5–2.1)</td>
<td>(0.8–1.8)</td>
<td>(0.6–6.5)</td>
<td>(0.9–2.1)</td>
<td>(0.9–2.4)</td>
<td>(1.1–90.1)</td>
</tr>
<tr>
<td>Wu-Williams et al, 1990&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Age, education, smoking, study area</td>
<td>–</td>
<td>1.4</td>
<td>–</td>
<td>2.1</td>
<td>–</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1.2–1.8)</td>
<td></td>
<td>(0.9–1.7)</td>
<td></td>
<td>(0.9–1.7)</td>
</tr>
<tr>
<td>Hinds et al, 1981&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Age, smoking, ethnic group</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.6–4.3)</td>
</tr>
</tbody>
</table>

† No adjustment for smoking as study on ‘non-smokers’ only, defined as persons who had smoked fewer than 100 cigarettes and had not used any other form of tobacco for more than six months

‡ Study involved adenocarcinoma only
1.4 SURVIVAL

Relative survival following a diagnosis of lung cancer, in the Australian states for which data were available, varied in the ranges of 10.1–11.1% in males and 12.3–13.7% in females at five years during the 1980s and 1990s. Recent Australian data for the period 1992–97 show a five-year relative survival for males of 11% and for females of 14%. These are compared with international figures in Table 5–1. When comparing survival and mortality data it should be noted that the denominator for survival is the population of patients with disease, whereas the denominator for the mortality rate from lung cancer is the whole population. Thus, the mortality rate may be low if there are a small number of cases with the disease, whereas poor survival results from patients with the disease dying relatively quickly.

Table 5–1 Five-year survival from lung cancer—international comparisons

<table>
<thead>
<tr>
<th>Males</th>
<th>Time period</th>
<th>Age group</th>
<th>Years after diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 yr</td>
</tr>
<tr>
<td>Australia</td>
<td>1992–97</td>
<td>All</td>
<td>34.6</td>
</tr>
<tr>
<td>New South Wales</td>
<td>1980–94</td>
<td>15–89</td>
<td>34.0</td>
</tr>
<tr>
<td>South Australia</td>
<td>1987–95</td>
<td>All</td>
<td>38.0</td>
</tr>
<tr>
<td>Queensland</td>
<td>1991–95</td>
<td>15–89</td>
<td>35.3</td>
</tr>
<tr>
<td>Western Australia</td>
<td>1994–97</td>
<td>15+</td>
<td>30.4</td>
</tr>
<tr>
<td>Europe</td>
<td>1985–89</td>
<td>15+</td>
<td>32.0</td>
</tr>
<tr>
<td>United States (SEER)</td>
<td>1991</td>
<td>All</td>
<td>38.9</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>Time period</th>
<th>Age group</th>
<th>Years after diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 yr</td>
</tr>
<tr>
<td>Australia</td>
<td>1992–97</td>
<td>All</td>
</tr>
<tr>
<td>New South Wales</td>
<td>1980–94</td>
<td>15–89</td>
</tr>
<tr>
<td>South Australia</td>
<td>1987–95</td>
<td>All</td>
</tr>
<tr>
<td>Queensland</td>
<td>1991–95</td>
<td>15–89</td>
</tr>
<tr>
<td>Western Australia</td>
<td>1994–97</td>
<td>15+</td>
</tr>
<tr>
<td>Europe</td>
<td>1985–89</td>
<td>15+</td>
</tr>
<tr>
<td>United States (SEER)</td>
<td>1991</td>
<td>All</td>
</tr>
</tbody>
</table>
Survival decreases with increasing age and extent of the disease. Data from New South Wales show five-year relative survival from localised lung cancer to be 23.2% compared with 1.0% of cases where the disease had spread to distant organs. Survival from SCLC is lower than that from NSCLC and it also varies by histological subtype, being higher from adenocarcinoma and squamous cell carcinoma than large cell (undifferentiated) carcinoma. Data from the South Australian hospital-based cancer registries showed five-year survival in 1987–95 to be 5% from SCLC, 20% from adenocarcinoma, 18% from squamous cell carcinoma and 8% from large cell carcinoma. Trends in survival from lung cancer since the 1980s have remained fairly poor, despite the improvement in survival from SCLC, which has occurred largely as a result of the introduction of chemotherapy in the 1970s.

References


SECTION II
PREVENTION AND DIAGNOSIS

2. PREVENTION AND SCREENING

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   - Self help
   - Pharmacological interventions
     - Nicotine replacement therapy
     - Antidepressants and anxiolytics
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2.2 Nutrition

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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 version\(^1\) in conjunction with a cost-effectiveness guidance\(^2\) as well as a shortened version\(^3\). 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 statement\(^6\). 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 interventions\(^7\), 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 clinics. 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 effective.

BEHAVIOURAL AND PSYCHOLOGICAL INTERVENTIONS

Both individual counselling and group therapy increase the chances of quitting. 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). 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 provider. 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 efficacy\textsuperscript{12}.

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)\textsuperscript{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)\textsuperscript{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 contact\textsuperscript{15}, 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 hypotension\textsuperscript{18}.

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 alone\textsuperscript{20}. 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-up\textsuperscript{21}.

<table>
<thead>
<tr>
<th>Guidelines – Strategies to Help People Stop Smoking</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective interventions include advice from doctors, structured interventions from nurses, and individual/group counselling.</td>
<td>1</td>
<td>8,9, 10, 11</td>
</tr>
<tr>
<td>Generic self-help materials are no better than brief advice, but more effective than doing nothing.</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Personalised materials are more effective than standard materials.</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>All currently available forms of nicotine replacement therapy are effective.</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Bupropion and nortriptyline increase effectiveness as evidenced by quit rates.</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Personalised smoking cessation advice for inpatients together with at least one month of follow-up increases quit rates.</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>
OTHER THERAPIES

A Cochrane review of 22 studies concluded that acupuncture was not superior to sham acupuncture in smoking cessation at any time point\(^22\). 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 interventions\(^23\). 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 cessation\(^24\). 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.

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

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 quitting\(^19\).
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 interviewing
- Concise, brief non-judgemental advice
- Arrange follow-up
- Enlist support
- Pharmacotherapy
- Refer to QUIT line
- Flagging smoking status on case notes of all attending patients
- Targeted to stage of change
- Use the five A’s.

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 1995. 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 intake.

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. Some micronutrients, such as the provitamin A carotenoids, vitamin C, vitamin E and selenium may inhibit carcinogenesis by functioning as antioxidants. However, while observational and biochemical studies indicated a protective effect for beta-carotene (a provitamin A carotenoid) 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.
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 quartile compared to the lowest quartile tends to be in the order of 1.3–2.0. In some studies, the relationship between fruit and vegetable consumption and lung cancer has varied according to sex, race, smoking history and histologic subtype. 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 cancer. 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 identified.

Since 1995, further studies on the relationship between nutrition and lung cancer have been completed, but have not altered the conclusions reached above. 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-cryptoxanthin. 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 tumours and is reinforced by molecular studies.
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. 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.

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) smokers.

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 years.
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 smokers\(^8\). However, a randomised chemoprevention trial found that isotretinoin (1mg/kg/day) was no better than placebo at reversing squamous metaplasia in bronchoscopic biopsies\(^9\).

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 subjects\(^9\). 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 months\(^9\).

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 NSCLC\(^9\). 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 × 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 smokers\(^9\).

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 mortality\(^9\). 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

<table>
<thead>
<tr>
<th>Guideline – Chemoprevention Strategies in Lung Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data do not support the use of currently reported chemoprevention strategies in lung cancer.</td>
<td>II</td>
<td>86,87,88, 89,90,91,92, 93,94</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Guideline – Dietary Supplementation with Beta Carotene</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet supplemented with pharmacological doses of beta-carotene increases the risk of lung cancer in heavy smokers.</td>
<td>II</td>
<td>82,83, 84,85</td>
</tr>
</tbody>
</table>

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 respectively\(^\text{101}\). 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\(^\text{102,103,104,105,106,107,108}\). These studies were all conducted in the 1960s and 1970s and the findings have been summarised in a recent systematic review\(^\text{109}\). 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 study\(^\text{110}\). 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 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 study. The results from extended follow-up of these studies have recently been reported\(^\text{111,112}\). 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 screening\(^\text{109}\).

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 years\(^\text{113}\).
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 mortality\(^{109}\).

<table>
<thead>
<tr>
<th>Guideline – Population Screening for Lung Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>I</td>
<td>108,111, 113,116</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>105,107, 110</td>
</tr>
</tbody>
</table>

**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 mortality\(^{115}\). 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 planned\(^{115}\).

In comparison to chest radiography, helical CT provides axial images of the lungs and mediastinum, with superior contrast resolution unhindered by superimposition of anatomical structures\(^{118}\). 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 1.1 mSv in women. This compares with 5.8 mSv for a conventional high-definition CT diagnostic examination and 0.015 mSv 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.

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) (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 2 cm 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 8 mm). 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’ outcomes.

Implementation of CT screening is critically dependent upon the availability of high-quality investigational procedures including fine needle aspiration (FNA) biopsies. 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 groups. There are indications that the cost per life year gained may be acceptable, but these depend on the assumptions made about benefits. 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 CT.

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 technique. 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.

One unanticipated benefit of ELCAP was a significant rate of smoking cessation (about 23%). 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.

<table>
<thead>
<tr>
<th>Guideline – Helical CT Screening</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>III–3</td>
<td>114, 122, 124, 126</td>
</tr>
</tbody>
</table>

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

**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 presentation. For some of these tests the test performance characteristics are currently being investigated in prospective studies. Other methods being investigated for the early detection of lung cancer...
include immunologic based screening of sputum and fluorescence bronchoscopy\textsuperscript{131}. 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 CT\textsuperscript{132}.

\noindent \textbf{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.

\noindent \textbf{References}


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 fibreoptic 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 treatment\(^1\). 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\(^2,3\).

<table>
<thead>
<tr>
<th>Guideline - Lung Cancer - Clinical Management</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All individuals with suspected lung cancer should be referred to a specialist with expertise in the management of lung disease for an opinion.</td>
<td>IV</td>
<td>1</td>
</tr>
</tbody>
</table>

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% metastases. 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 malignant.

The majority of individuals with lung cancer have symptoms at diagnosis. 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 benign.

- **Calcification is the single best morphological indicator of a benign lesion** (II-O). CT detects calcification more accurately than chest x-ray (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 diagnosis (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 SPNs.** 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%.** 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 diagnosis\textsuperscript{14}, 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 specimens\textsuperscript{15}. 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 sputum\textsuperscript{16} and optimal processing\textsuperscript{17} also increases the sensitivity of sputum cytology for the detection of lung cancer.

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

<table>
<thead>
<tr>
<th>Guidelines - Lung Cancer - Sputum Cytology</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum cytology is recommended to help establish a positive diagnosis of lung cancer in individuals with a central pulmonary mass.</td>
<td>III-(O)</td>
<td>16,17</td>
</tr>
</tbody>
</table>

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%\textsuperscript{19,20}. For SPNs the negative predictive value of FNA has been reported as ranging from 52–84%\textsuperscript{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\textsuperscript{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.

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

**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. 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 histoplasmosis. This is an important consideration when PET is used to select individuals for curative surgery (see below).

<table>
<thead>
<tr>
<th>Guideline – Lung Cancer – PET Scanning in Diagnosis</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>I–(O)</td>
<td>31,32,33</td>
</tr>
</tbody>
</table>

### 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. In the assessment of chest wall invasion, the overall accuracy of CT has been reported to be 39–86%. 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.

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.

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 planning.

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 1 cm is considered pathological. 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. Similar diagnostic accuracy has been reported with MRI.

Because CT assessment incorrectly over-stages or under-stages T and N status in up to 40% of cases some form of surgical sampling is required to confirm the CT results. The value of mediastinoscopy as a staging procedure is widely accepted, 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. Anterior mediastinotomy allows access to some nodes that cannot be sampled by mediastinoscopy.

<table>
<thead>
<tr>
<th>Guideline – Staging Non-small Cell Lung Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with mediastinal nodes larger than 1 cm in transverse diameter on CT who otherwise have resectable lung disease should undergo further staging evaluation.</td>
<td>I–(O)</td>
<td>51,54</td>
</tr>
</tbody>
</table>
PET staging of N status has an accuracy of around 90% (81–99% reported), sensitivity of 80–100% and specificity of 90–99%. A mean sensitivity of 79% and specificity of 91% for PET, and 60% and 77% respectively for CT, were reported in a meta-analysis. FDG PET has also been shown to separate N2 and N3 disease reliably.

The high negative predictive value of PET in mediastinal staging allows patients with a negative scan to proceed to thoracotomy without invasive mediastinal staging. 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.

<table>
<thead>
<tr>
<th>Guideline – PET Scanning in Staging Non-small Cell Lung Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>I–(O)</td>
<td>51,58,59</td>
</tr>
</tbody>
</table>

**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 presentation and many of these do not have extensive local disease. There is a correlation between T and N stage and the presence of metastases with squamous cell carcinoma but not with large cell or adenocarcinoma.

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 asymptomatic. Also postmortem studies of patients who died in the peri-operative period following curative surgery, and PET studies of individuals staged by conventional methods as M0, have shown occult metastases in about 20%.

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.

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 uncommon and the impact of CT of the liver on M staging is low. Adrenal lesions are frequently seen, but two thirds are adenomas. Chemical shift MRI imaging is reliable...
in differentiating adenomas from adrenal metastases when CT findings are equivocal. Other alternatives include CT densitometry using non-enhanced CT attenuation of the lesions, washout of CT contrast enhancement 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 bone scan or MRI are useful modalities to investigate suspected bony metastases. Because the incidence of occult bony metastases is less than 4%, 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. 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 modality.

PET is more accurate in the detection of metastatic disease in adrenal glands and the skeleton compared to CT and radionuclide bone scan. Occult extrathoracic metastases were detected in up to 24% of patients by whole body FDG PET. 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. PET staging has been found to be a powerful predictor of survival and translates to more superior prognostic stratification compared to conventional staging methods.

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:

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

| 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. 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 required.

<table>
<thead>
<tr>
<th>Guideline – Staging – Small Cell Lung Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>II</td>
<td>87</td>
</tr>
</tbody>
</table>

### 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 factors and a consensus statement 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 resection. 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.

The UICC’s publication on prognostic factors divides them into three categories: disease related, patient related and environment related. It further recognises that there may be differences in the prognostic significance of some factors depending on disease extent and type of treatment.
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 surgery\(^9^4\) and chemoradiotherapy\(^9^5\) in institutions with greater experience.

<table>
<thead>
<tr>
<th>Guideline – Non-small Cell Lung Cancer – Prognosis</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
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<tbody>
<tr>
<td>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.</td>
<td>IV</td>
<td>88</td>
</tr>
</tbody>
</table>

**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 metastases\(^8^8\). Performance status is an essential host related factor, with age, sex and weight loss as additional factors\(^8^8,^9^6\).
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.

### 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 information 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 markers. 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 appointments. 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

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.

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Refs</th>
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</thead>
<tbody>
<tr>
<td>IV</td>
<td>98</td>
</tr>
</tbody>
</table>

References


SECTION III
PATIENT SUPPORT AND DEFINITIVE TREATMENT

4. SUPPORTING THE PATIENT DURING DIAGNOSIS AND TREATMENT

4.1 Information provision
4.2 Prevalence of anxiety, depression and distress
4.3 Quality of life
4.4 Counselling, support and psychological treatments
   Social support
4.1 INFORMATION PROVISION

The diagnosis and treatment of lung cancer is a major stressful life event for every individual afflicted and requires an adaptive adjustment to sustain quality of life. Attention to information provision and communication with the patient, to their psychological adaptation and their social needs are fundamental dimensions of care that will enhance their quality of life while striving to prolong survival.

Consumer satisfaction surveys of patients with cancer repeatedly identify information provision as a major source of unmet needs\(^1\). A meta-analysis of educational interventions in cancer has shown that the provision of adequate information is related to increased psychological wellbeing\(^2\). Effective communication skills ensure that this information is clearly explained and understood\(^3\).

Studies have shown that only part of the initial consultation is remembered\(^5\). Therefore clinicians need to recognise that the integration of information is a gradual process that requires both time and the opportunity to ask questions at subsequent visits. It is not necessary to make treatment decisions at the initial consultation unless the patient clearly chooses to do so. For non-English patients, professional interpreter services should be used and use of family members as interpreters avoided.

When breaking bad news, two points are particularly important: firstly, care should be taken to deliver the information in language that the patient understands and secondly, appropriate support, including the attendance of significant others, if desired by the patient, should be provided. Tape recording of such sessions should be routinely offered\(^6\). The NHMRC recommends the following approach for breaking bad news, adapted from The Cancer Council New South Wales\(^1\):

- give bad news in a quiet, private place
- allow enough uninterrupted time in the initial meeting
- assess the individual's understanding
- provide information simply and honestly
- encourage individuals to express their feelings
- respond to individual's feelings with empathy
- give a broad time-frame for the prognosis
- avoid the notion that nothing can be done
- arrange a time to review the situation
- discuss treatment options
- offer assistance to tell others
- provide information about support services
- provide written information
- offer a tape recording of the session.
In our society, most patients wish to be fully informed of all available information, and usually want a close relative or friend present during this interview. In general, cancer patients should be invited to guide the clinician about the level of detail they wish to receive and their desire for active involvement in decision making. Discussion of the actions that can be taken and what the diagnosis means, are at least, if not more, important than the disclosure of the initial diagnosis. The clinician’s choice of words is critical, as being deliberately vague or using euphemisms can significantly impair communication.

Clinicians should review both the patient’s understanding of what they have been told and their reaction to this news, as a means of increasing integration of this information and providing emotional support. Patients are entitled to make their own decisions about treatments or procedures, but need adequate information on which to base these decisions. One study of patients with lung cancer found that 29% perceived a discrepancy between their desired role in decision making and their actual role. Nearly two thirds sought an active, collaborative decision making style. Clinicians should provide information in a form and manner that helps the patient to understand the treatment options available, and which is tailored to the patient’s circumstances, personality, level of education and understanding, expectations, fears, beliefs, values and cultural background.

In regard to prognosis, a study of patients with metastatic incurable cancer revealed that the information most sought by patients included longest survival time with treatment, five-year survival rates, and average survival. Words and numbers were preferred to graphs.

There can be difficulty in comparing results between studies as the outcome may be reported in different ways. For instance survival outcomes can be reported as a percentage of survival at a particular time point, for example, one-year or five-year survival rates, median survival, survival curves, or hazard ratios. Each of these provides different information, and discussion of prognosis may require all of these factors to be discussed in an easily comprehensible fashion that is applicable to the individual.

<table>
<thead>
<tr>
<th>Guidelines – Informing the Patient</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients should be provided with adequate information, as this is associated with enhanced patient psychological wellbeing.</td>
<td>III–3</td>
<td>2</td>
</tr>
<tr>
<td>Clinicians should follow the NHMRC recommended guidelines on the breaking of bad news, providing information about treatments and the discussion of prognosis.</td>
<td>IV</td>
<td>1</td>
</tr>
</tbody>
</table>
4.2 PREVALENCE OF ANXIETY, DEPRESSION AND DISTRESS

Studies screening patients with lung cancer for evidence of psychological distress have reported rates between 15%\textsuperscript{14} and 25%\textsuperscript{15}. As the disease becomes more advanced, these rates climb as high as 69%\textsuperscript{16}. Studies specifically seeking to identify anxiety disorders have recorded rates between 13% and 50%\textsuperscript{17,18,19}, while those delineating depressive disorders have identified rates between 9% and 36%\textsuperscript{17,18,20,21,22}.

In an important study conducted by the British Medical Research Council Lung Cancer Working Party, depression was identified in 33% of patients (n=322) before treatment and persisted in more than 50% of patients following treatment. Small cell lung cancer patients had a three-fold higher prevalence of depression than NSCLC patients\textsuperscript{22}.

In an Australian study of patients with advanced cancer in the palliative care setting, up to half of the patients, one third of their spouses and one quarter of their offspring showed evidence of substantial psychological distress warranting specific support\textsuperscript{23}. The distress reverberates through the family in this setting, such that both patient- and family- centred models of care need to be utilised.

Predictors of anxiety and depressive disorders in patients with lung cancer include poor performance status\textsuperscript{22,24}, poorly treated pain\textsuperscript{16}, female gender\textsuperscript{22,25} (especially with early stage disease), living alone, lacking confidants and having a hopeless/helpless coping attitude\textsuperscript{25}. Pretreatment physical symptom burden, fatigue and physician-rated performance status were also independent predictors of depression, but histological subtype was not\textsuperscript{22}.

Meta-analyses to evaluate the efficacy of treatment of anxiety and depressive disorders in patients with cancer have demonstrated the importance of recognition and treatment of these medical problems\textsuperscript{2,26,27}. Trials of antidepressants in cancer populations show the same level of efficacy as that seen in the treatment of depression in non-cancer populations\textsuperscript{28,29}.

<table>
<thead>
<tr>
<th>Guideline – Psychosocial Care in Lung Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is critical to recognise distress, anxiety and depressive disorders in patients with lung cancer as treatment with combined pharmacotherapy (antidepressants) and psychotherapy is efficacious.</td>
<td>I</td>
<td>2,26,27</td>
</tr>
</tbody>
</table>
4.3 QUALITY OF LIFE

Examination of symptoms at presentation and during treatment for lung cancer show the pattern to be virtually the same for patients with SCLC and NSCLC. Prominent symptoms that affect quality of life include disease-related chest symptoms (shortness of breath, cough and pain); constitutional symptoms (fatigue, anorexia); and psychological concerns (insomnia, decreased libido, worry). In addition, prophylactic cranial irradiation is associated with a transient increase in sickness and vomiting. Studies have varied in their conclusion as to the effect of chemotherapy on quality of life. One study in SCLC showed a diminishing of quality of life with continuing chemotherapy for regimens such as cyclophosphamide/vincristine/etoposide (level II evidence), and this burden of treatment needs to be balanced against tumour response. However, several studies comparing chemotherapy with best supportive care in advanced NSCLC have shown maintenance or improvement in measures of quality of life.

The routine use of computerised quality of life screening using typical scales such as the European Organization for Research and Treatment of Cancer (EORTC) QLQ–C30 has not been shown to improve outcome in patient wellbeing or satisfaction with care in patients with lung cancer. This contrasts with screening for depression or distress, which does generate a significant clinical improvement.

<table>
<thead>
<tr>
<th>Guideline – Quality of Life in Lung Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>The potential impact of treatment on quality of life in patients with lung cancer should be included in discussions of treatment alternatives.</td>
<td>II</td>
<td>18,30,31, 32,33,34</td>
</tr>
</tbody>
</table>

4.4 COUNSELLING, SUPPORT AND PSYCHOLOGICAL TREATMENTS

A range of psychological therapies is available to assist in enhancing coping and relieving distress in patients with lung cancer. These interventions can be delivered individually or via group or family approaches, and follow well described models of psychotherapy including the supportive-expressive, cognitive-behavioural, interpersonal, existential and psychodynamic schools of psychotherapy. They enhance emotional adjustment (sense of control, self esteem, living with uncertainty, fear of death, complicated grief and depression); improve functional status (activities of daily living, social and role functioning, vocational activities); improve knowledge of lung cancer and its treatment; improve treatment- and disease-related symptoms (for example, nausea, vomiting, pain etc); and increase overall quality of life. Meta-analyses have confirmed the benefits of these psychological treatments in various cancers.
Relaxation-based therapies provide benefits by reducing anxiety, treatment-related phobias such as needle phobia, conditioned nausea and vomiting, and insomnias. Existential distress, which finds expression in fear of the reality or process of dying, essential aloneness, meaninglessness and unrealistic fears about the processes of treatment, can be ameliorated with supportive-expressive or cognitive-behavioural therapies. Furthermore, compliance with medical therapies can be improved. Early referral for specialist support from a clinical psychologist or consultation-liaison psychiatrist is worthwhile when symptoms of distress or high risk for psychiatric morbidity become evident.

Randomised controlled trials of early versus late referral to palliative care services show strong evidence of the benefits of early referral in reducing time spent in hospital, enhancing symptom control, increasing family satisfaction and permitting death to occur in the desired location. Early referral to community-based domiciliary palliative care services, where available, may have several benefits and enhance quality of life.

<table>
<thead>
<tr>
<th>Guideline – Psychosocial and Supportive Services in Quality of Life in Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological interventions and early referral to psycho-oncology and palliative care services improves quality of life in patients with cancer.</td>
<td>I</td>
<td>2,26,27</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>38,39</td>
</tr>
</tbody>
</table>

**SOCIAL SUPPORT**

A number of people involved in the patient’s care may be involved in providing support in either a formal or informal manner. These can include family, friends, doctors, nurses, and other health care professionals, and together form the treatment team. Co-ordination and continuity of care ensure high quality treatment for patients with lung cancer. The choice of the person to co-ordinate this care should be made by the patient in conjunction with their general practitioner and specialists. This co-ordinator need not necessarily be a health professional.

Assistance with transport, care of children or other family members, home support, respite care and volunteer assistance are some of the many means of social support. State and Territory Cancer Councils provide support through a telephone help line (the national telephone contact number for all such services is 13 11 20). Professional guidance or the support of volunteers is available through such services, together with information about local community self-help groups and related services. Regional Cancer Councils offer a range of educational pamphlets to assist patients and their families.
In summary, the social support needs for patients with lung cancer and their families include:

- access to cancer support services and community self-help groups
- information about community social support resources
- assistance with transport, child care, home help
- guidance about financial and disability support.

References


12. NHMRC General guidelines for medical practitioners on providing information to patients. 1994. Canberra, AGPS.


5. NON-SMALL CELL LUNG CANCER

5.1 Management of non-small cell lung cancer by stage

5.2 Surgery
Surgical resection for early stage disease (clinical Stages I and II)
Extent of pulmonary resection
Nodal assessment

5.3 Radiotherapy
Radiotherapy in the treatment of locoregional non-small cell lung cancer
   Dose of radiotherapy
   Duration of radiotherapy
   Radiotherapy versus radiotherapy plus chemotherapy
   Chemotherapy versus radiotherapy with or without chemotherapy
   Timing of chemotherapy/radiotherapy regimens
   Frequency of chemotherapy
   Cisplatin or carboplatin
Radiotherapy or surgery for Stage III disease
Postoperative radiotherapy
Complications of thoracic radiotherapy

5.4 Chemotherapy and adjuvant or neo-adjuvant treatment of locoregional non-small cell lung cancer
   Surgery and adjuvant chemotherapy
   Surgery and neo-adjuvant chemotherapy

5.5 Chemotherapy in advanced/metastatic non-small cell lung cancer
   General aspects
   The role of systemic chemotherapy in advanced non-small cell lung cancer
   Appropriate chemotherapy for treating advanced non-small cell lung cancer
      Single agent versus combination chemotherapy
   Optimal combination chemotherapy for advanced non-small cell lung cancer
      ‘New’ versus ‘old’ combinations with platinum
      Cisplatin versus carboplatin trials
      Trials comparing ‘new’ drug plus platinum combinations
      Non-platinum new drug combinations
   Appropriate dose and duration of chemotherapy
   The role of second-line chemotherapy and other agents in advanced non-small cell lung cancer
   Biological agents
5.1 MANAGEMENT OF NON-SMALL CELL LUNG CANCER BY STAGE

The optimal treatment for lung cancer is surgery. This approach implies that the tumour is at an early stage and that the patient is suitable for optimal regimen. When the disease is more advanced and technically unresectable, or the patient is not fit for surgery, radiotherapy, chemotherapy or palliation are appropriate. Table 1–5 provides pathways for care.

Table 1–5 Management of non-small cell lung cancer stage by stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Optimal regimen</th>
<th>If patient is not suitable for optimal regimen, treat depending on symptoms and performance status</th>
</tr>
</thead>
</table>
| Stages I & II | Surgical resection | Radical radiotherapy +/- chemotherapy (good performance status)  
 or  
Palliative management (poor performance status)  
 or  
Observation if not symptomatic |
| Stage IIIA | Induction chemotherapy  
→ Surgical resection  
→ +/- Mediastinal radiotherapy  
 or  
Radical combination chemoradiotherapy | Palliative radiotherapy or chemotherapy  
 or  
Observation if not not symptomatic |
| Stage IIIB | Radical combination chemoradiotherapy | |
| Stage IV | Chemotherapy and  
Palliative radiotherapy for specific sites of disease (brain, bone pain).  
Some patients with solitary brain metastases may be suitable for surgical excision | Palliative radiotherapy  
 or  
Supportive care alone |
5.2 **SURGERY**

**SURGICAL RESECTION FOR EARLY STAGE DISEASE**

**(CLINICAL STAGES I & II)**

Surgical resection has been shown to result in the best five-year disease-free survival rates compared to any other form of treatment for NSCLC. Since the first successful pneumonectomy for NSCLC by Dr Evarts Graham in St Louis in 1933, there have been refinements in patient selection, operative techniques and perioperative management which have translated into better survival with reduced postoperative morbidity and mortality.

In looking at historical series of early stage lung cancer survival, it must be remembered that there has been a great variation in the degree of characterisation of metastases and node staging from the techniques used for the evaluation (including CT scanning, PET scanning, routine or selective mediastinoscopy, node sampling or node dissection at operation) as well as the difficulties of naming mediastinal and hilar node disease according to whichever node map was utilised. A recommendation for node classification was revised in 1997 and this is currently used in Australia for description of node locations both anatomically and pathologically.

Lung cancer survival following surgical resection was reviewed by Rubins comparing those patients treated between 1947–69 with those treated between 1981–94. This demonstrated that stage for stage the survival over the 47-year period had not altered but the operative mortality had reduced markedly.

Surgery outperforms radiation therapy in the treatment of early stage NSCLC in those patients fit enough to tolerate the required resection. Morrison reported a randomised study comparing radical radiation employing 45Gy in four weeks for early stage disease versus surgical resection. At four years there was a reported 7% survival in the radiation group compared to 23% in the surgical group. Gauden reported the largest retrospective study of radiation for early stage lung cancer demonstrating a five year recurrence-free survival of 23% with the median survival being 19.5 months, significantly less than that reported in comparable surgical series for non-small cell lung cancer.

The Japanese Lung Cancer Screening Research Group studied 69 patients with Stage I lung cancer treated non-surgically with either chemotherapy or radiotherapy and found the five-year survival to be 14.3% in screen-detected asymptomatic patients and 3.7% for symptomatic patients. This study emphasised the poor prognosis for Stage I NSCLC patients treated without surgical resection.

Many reviews have been published supporting surgery as the preferred form of treatment for early stage non-small cell lung cancer. The overall reported survival for patients with pathological Stage I and II disease is as follows:
Table 2–5  Survival for patients with stage 1 and 2 non-small cell lung cancer\textsuperscript{12}

<table>
<thead>
<tr>
<th>Pathological stage</th>
<th>Five-year survival (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td></td>
</tr>
<tr>
<td>T1 N0</td>
<td>76.0% (68–83%)</td>
</tr>
<tr>
<td>T2 N0</td>
<td>59.5% (54–65%)</td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
</tr>
<tr>
<td>T1 N1</td>
<td>51.9% (40–63%)</td>
</tr>
<tr>
<td>T2 N1</td>
<td>40.3% (39–45%)</td>
</tr>
<tr>
<td>T3 N0</td>
<td>38.0% (25–55%)</td>
</tr>
</tbody>
</table>

EXTENT OF PULMONARY RESECTION

The extent of pulmonary resection required to yield the optimal survival rates has been reviewed since the first successful pneumonectomy in 1933. Pneumonectomy was initially thought necessary for potential cure but survival data reported in the 1950s indicated that lobectomy was equally effective provided both macroscopic and microscopic clearance of tumour was achieved. Lobectomy was associated with lower operative and long-term mortality and morbidity compared with pneumonectomy.

Lobectomy with mediastinal lymph node dissection is now the gold standard for surgical resection of NSCLC. Pneumonectomy is appropriately reserved for those patients with centrally placed primary tumours crossing the interlobar fissure, involving the main stem bronchi or main pulmonary arteries or in the presence of malignant hilar nodal disease in Stage II NSCLC. For patients with direct invasion of structures adjacent to the lung (T3: parietal pleura, chest wall, pericardium, diaphragm) en bloc resection of lung and involved extra pulmonary structures is associated with five-year survival in excess of 50% in those in whom complete microscopic resection is achieved and the nodal status is NO\textsuperscript{13,14}.

As with malignancies elsewhere in the body, thoracic surgeons have assessed the role of lesser resections, namely pulmonary segmentectomy or wedge resections, for early stage NSCLC. In a retrospective review Warren and Faber\textsuperscript{15} recorded 173 patients with Stage I NSCLC who had undergone either lobectomy or segmental resection. The five-year survival was similar, but there was a significant increase of locoregional recurrence in the segmental resection group (23%) compared to those undergoing lobectomy (5%).
The Lung Cancer Study Group\textsuperscript{16} in a prospective, multi-institutional randomised trial compared lobectomy with minimal resection, most commonly segmentectomy. All patients were assessed as fit for lobectomy, and randomised in the operating theatre after frozen section confirmed T1 N0 staging with hilar and mediastinal lymph node sampling. Two hundred and forty seven patients were randomised. In those patients randomised to limited resection there was a significantly increased local recurrence rate, as well as an increased mortality rate related to their lung cancer. The study concluded that “because of the higher death rate and a locoregional recurrence rate associated with limited resection (either segmentectomy or wedge resection), lobectomy still must be the surgical procedure of choice for patients with peripheral T1 N0 NSCLC”\textsuperscript{16}.

Ichinose\textsuperscript{17} studied the correlation of tumour size with lymphatic invasion in resected peripheral Stage I NSCLC and found that as the tumour increased in size, the chance of lymphatic invasion increased from 25\% in tumours less than 1cm in diameter to 57\% in tumours greater than 3.1cm in diameter. This study emphasised the benefit of lobectomy over lesser resections in Stage I NSCLC.

Furthermore, limited resections are not appropriate for patients with Stage I NSCLC who have adequate pulmonary function for lobectomy. The operative approach for lobectomy has traditionally been via a thoracotomy. Recently video-assisted thoracoscopic techniques (VATS) have been utilised successfully for pulmonary resections including regional lymph node assessment. Sugii\textsuperscript{18} studied 100 consecutive patients with clinical Stage IA (T1 N0) NSCLC. Forty-eight patients underwent VATS lobectomy and 52 patients open lobectomy; lymph node dissection was performed in both groups. There were no differences in local recurrence rates (6\%) or five-year survival (90\% VATS, 85\% open) between the two groups. Further studies are required to provide definitive evidence on the relative effectiveness and safety of lobectomy via VATS as compared with open thoracotomy.

<table>
<thead>
<tr>
<th>Guideline – Non-small Cell Lung Cancer – Lobectomy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy is preferred to limited resection in patients with operable T1 N0 NSCLC.</td>
<td>II</td>
<td>16</td>
</tr>
</tbody>
</table>

**NODAL ASSESSMENT**

Intra-operative and subsequent pathological regional node examination, as with most malignancies, is important in the management of NSCLC. There has been controversy regarding the extent of lymph dissection necessary for optimal results.

Asamura\textsuperscript{19} demonstrated that if extensive lymph node sampling is performed, 25\% of patients are found to have unsuspected positive nodes (N1 10\%, N2 15\%). In patients with positive mediastinal nodes 25\% had no hilar node involvement. In Asamura’s series, Stage I patients had a five-year survival of 92\% and a ten-year survival of 87\%.
However, the study could not definitively relate the increased survival identified in these Stage I patients as being due to the lymph node resection, as opposed to simply more accurately identifying those patients that were truly Stage I disease.

There has also been debate over whether mediastinal lymphadenectomy has a therapeutic advantage for resected lung cancer. Izbicki et al\textsuperscript{20} randomised 182 patients with NSCLC to either standard mediastinal lymphadenectomy (removal of lymph nodes suspected of being involved in the hilar or mediastinal regions) or en bloc radical mediastinal lymphadenectomy (as described by Naruke et al\textsuperscript{21}), where all tissue containing mediastinal lymph nodes is removed and en bloc skeletonising of the mediastinum is performed. When matched to T and N status, no difference in survival, site or recurrence was shown. Not surprisingly, staging was more detailed in the radical lymph node dissection group.

A prospective randomised study by Sugi\textsuperscript{22} studied 115 patients with peripheral NSCLC less than 2cm in diameter. Patients were randomly assigned to lobectomy with lymph node sampling or lobectomy with radical systematic lymph node dissection. There was no difference in the detection of N1 or N2 positive nodes, no difference in either the local, distant or recurrence rates or in the five-year survival between the two groups (84\% for node sampling group and 81\% in the node dissection group).

<table>
<thead>
<tr>
<th>Guideline – Non-small Cell Lung Cancer – Regional Lymph Node Assessment</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional lymph node assessment should be performed with all lung resections for NSCLC. Radical mediastinal lymph node dissection whilst more accurately staging the patient provides no significant survival advantage over appropriate mediastinal lymph node sampling.</td>
<td>II</td>
<td>19,20,22</td>
</tr>
</tbody>
</table>
5.3 RADIOTHERAPY

RADIOTHERAPY IN THE TREATMENT OF LOCOREGIONAL NSCLC

It has been known for many years that ionizing radiation is capable of killing lung cancer cells and reducing tumour size. In 1932, Pancoast described responses of tumours treated with radiotherapy, but acknowledged that the results “for the most part, have been discouraging”\(^\text{23}\). In 1955, Bromley and Szur were able to confirm Pancoast’s original observations through histopathologic examination of 66 lung cancers that were irradiated before resection. Although 17% of the cancers were of the oat cell variety, no tumour was found in 29 of 62 (46.7%) specimens examined\(^\text{24}\). These findings led to uncertainty about the relative values of surgical resection and radiotherapy in the management of operable lung cancer, which was subsequently resolved by a randomised trial conducted at the Hammersmith Hospital. This study showed a statistically significant survival benefit for patients randomised to have radical surgery compared with patients randomised to have radiotherapy (45Gy of megavoltage irradiation), particularly for the subgroup with squamous cell carcinoma\(^4\). The Hammersmith trial has had a profound influence on subsequent practice such that surgery came to be, and is still regarded as, the treatment of choice for fit patients with resectable lung cancer.

Subsequent studies were designed to examine the value of radiotherapy in the management of patients with inoperable NSCLC, in particular, to determine whether the locoregional cytotoxic effects of radiotherapy translate into a survival advantage compared with placebo or a policy of observation\(^\text{25,26,27}\). Three randomised trials designed to test this hypothesis have been published. One large North American study conducted by the Veterans Administration Lung Cancer Study Group (VALCSG), involving 800 patients, revealed a small but statistically significant advantage for patients with pathologically proven lung cancer confined to the chest who were randomised to radiotherapy compared with placebo\(^\text{25}\). Patients with SCLC were included in this study, but subset analysis indicated that the survival advantage was essentially confined to patients with non-small cell histology/cytology. Two smaller European studies, which included radiotherapy and observation as two of the treatment arms, failed to reveal a survival advantage associated with the use of immediate radiotherapy\(^\text{26,27}\). Not only were these studies smaller than the VALCSG study (249 and 117 patients respectively), and less likely to detect a difference between treatment policies, one study (unlike the VALCSG study), included patients without pathological confirmation of the diagnosis\(^\text{25}\), and the other closed prematurely because of poor accrual\(^\text{26}\).
In patients with inoperable NSCLC and who have no evidence of distant metastases, radiotherapy is recommended to locoregional disease because it may be associated with a survival advantage compared with placebo.

**DOSE OF RADIOTHERAPY**

The influence of radiotherapy dose on survival in patients with good performance status who have locoregional inoperable NSCLC has been investigated in four randomised trials. A dose of 60Gy given over six weeks was shown to be associated with an improved response rate, but not survival, compared with lower doses in a study of the Radiation Therapy Oncology Group (RTOG). Importantly, the higher dose did not appear to be associated with increased toxicity. Similarly, no improvement in survival was observed when doses of 50Gy versus 42Gy and 50Gy versus 40Gy were compared. A British study showed a small but statistically significant survival benefit for 39Gy versus 17Gy. A comparison of hyperfractionated radiotherapy (69.6Gy given as 1.2Gy fractions, twice a day) revealed no advantage compared with 60Gy given by conventional fractionation, and that the hyperfractionated schedule was significantly inferior to combined modality treatment with chemotherapy and radiotherapy.

In patients with locoregional inoperable NSCLC and with good performance status, higher doses of radiotherapy are associated with better response and possibly survival. Doses in the vicinity of 60Gy in six weeks are recommended because they are safe and give the highest response rates.

**DURATION OF RADIOTHERAPY**

It has recently been recognised that prolonging the time over which some epithelial cancers are treated with radiotherapy reduces the probability of local control, most likely by allowing accelerated repopulation of surviving clonogens. To minimise the chance of this occurring, treatment schedules that reduce overall treatment time (accelerated radiotherapy) have been designed and tested. The best known is the CHART (continuous hyperfractionated accelerated radiotherapy) regimen, in which
36 treatments are given in a 12 day period, with six hour intervals between treatments and without weekend interruption. The CHART schedule was shown to be superior to conventionally fractionated radiotherapy in a large multicentre trial, with a 22% reduction in relative risk of death across all patients and a 30% reduction in risk of death for patients with squamous cell carcinoma. This trial included patients with Stage I and II disease, for whom a similar reduction in risk was observed as for patients with more advanced disease. The better survival was due predominantly to improved local control, thus providing proof of the principle that radiotherapy can increase survival in selected patients with NSCLC.

The combination of chemotherapy and radiotherapy is also associated with a survival advantage (see following section). Only one study has directly compared accelerated radiotherapy with combined chemotherapy and radiotherapy. This was a small study with less power than the CHART study to detect a survival advantage, and there was no clear benefit for any of the treatment arms. Thus, it remains unclear whether the survival advantage associated with CHART is of a greater magnitude than that achievable with combined chemotherapy and radiotherapy. As the main drawback associated with the CHART regimen is the timing of much of the treatment outside normal working hours, its use is unlikely to be widely adopted unless it can be shown to have significant advantages over combined chemotherapy and radiotherapy.

RADIOTHERAPY VERSUS RADIOTHERAPY PLUS CHEMOTHERAPY

Using survival as the endpoint, two meta-analyses have established the superiority of combined cisplatin-based chemotherapy and radical radiotherapy over radical radiotherapy alone. No survival advantage was observed if the chemotherapy did not contain cisplatin. The magnitude of the effect was similar for patients with Stage I or II disease as well as for those with Stage III disease. The benefit was most evident in patients with good performance status. A survival advantage was also observed in patients with poor performance status but this was not statistically significant.

<table>
<thead>
<tr>
<th>Guideline – Non-small Cell Lung Cancer – Radiotherapy and Chemotherapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>The combination of cisplatin-based chemotherapy and radical radiotherapy in patients with good performance status is associated with a small but significant survival advantage compared with radiotherapy alone in NSCLC.</td>
<td>1</td>
<td>35,36</td>
</tr>
</tbody>
</table>

The combination of cisplatin and radical radiotherapy was associated with a 13% reduction in risk of death, translating into an absolute survival benefit of 4% at two years and 2% at five years.
CHEMOTHERAPY VERSUS RADIOThERAPY WITH OR WITHOUT CHEMOTHERAPY

There are a number of studies in which radiotherapy and chemotherapy have been compared directly, but in none of these has a survival advantage been demonstrated for one treatment modality over the other\textsuperscript{26,37,38,39}.

When the combination of radiotherapy and chemotherapy was compared with chemotherapy alone, in a small Japanese study of patients with Stage III disease who responded to initial cisplatin-based chemotherapy, there was a significant survival advantage for patients having the combined treatment\textsuperscript{40}. However, in a larger European study of similar design (patients without evidence of distant metastases who had responded to chemotherapy were randomised to further chemotherapy, or to radiotherapy), the addition of radiotherapy to chemotherapy did not significantly influence survival compared with chemotherapy alone, although it did result in significantly better local control\textsuperscript{41}.

TIMING OF CHEMOTHERAPY/RADIOThERAPY REGIMENS

In a meta-analysis, all but one of eleven cisplatin trials had employed sequential chemotherapy followed by radiotherapy\textsuperscript{35}. Seven comparisons of concurrent cisplatin/radiotherapy and six comparisons of sequential treatment were found to be associated with similar reductions in risk of death in a later meta-analysis\textsuperscript{36}. Two recent studies published since the meta-analyses comparing concomitant chemotherapy and radiotherapy with sequential chemotherapy followed by radiotherapy have revealed a survival advantage in favour of concurrent treatment\textsuperscript{42,43}.

<table>
<thead>
<tr>
<th>Guideline – Non-small Cell Lung Cancer – Timing of Radiotherapy and Cisplatin Therapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant cisplatin and radiotherapy are associated with a better survival than if the two treatments are given sequentially.</td>
<td>II</td>
<td>42,43</td>
</tr>
</tbody>
</table>

FREQUENCY OF CHEMOTHERAPY

The original European Organization for Research and Treatment of Cancer (EORTC) study, which demonstrated a survival advantage for the concomitant daily administration of cisplatin compared with radical radiotherapy alone, had a third arm in which patients were randomised to have weekly cisplatin\textsuperscript{44}. The survival in this arm was intermediate between the other two arms, but was not significantly different from either.
CISPLATIN OR CARBOPLATIN

Both cisplatin and carboplatin have been shown to potentiate radiation-induced cytotoxicity in human lung cancer cell lines in preclinical studies. The effects of carboplatin are similar to those of cisplatin, but of a slightly lower magnitude. Carboplatin, however, has less neurological, renal and gastrointestinal toxicity than cisplatin. The combination of radical radiotherapy and concomitant carboplatin has been tested against radiotherapy alone, but not against cisplatin and radical radiotherapy. Two studies have shown a survival advantage for the combination of carboplatin and hyperfractionated radiotherapy. Three other studies were inconclusive, showing no clear benefit for the addition of concomitant carboplatin to radiotherapy.

RADIOThERAPY OR SURGERY FOR STAGE III DISEASE

Locally advanced disease characterised by mediastinal lymph node involvement (N2) is usually treated by radiotherapy. Recently there has been increasing interest in the use of surgery in patients with this disease stage, particularly with the demonstration of a survival advantage in two small randomised trials of chemotherapy followed by surgical resection (with and without postoperative radiotherapy) compared with locoregional treatment alone. However, in two small trials, the same strategy of preoperative chemotherapy and surgery was compared with radiotherapy and with chemotherapy followed by radiotherapy, and there was no evidence of a survival advantage for either approach.

POSTOPERATIVE RADIOTHERAPY

The role of postoperative radiotherapy in patients who have had complete resection of NSCLC has recently been evaluated by meta-analysis. This revealed that in patients with Stage I or II disease, postoperative radiotherapy was detrimental to survival, compared with patients randomised to surgery alone. In patients with Stage III disease the effect of radiotherapy on survival was inconclusive. However, radiotherapy did appear to be associated with a reduction in local recurrence. It is possible that if smaller volumes of normal lung are irradiated using more modern radiotherapy techniques, the improvement in local control might result in a survival advantage. Postoperative radiotherapy using these techniques in patients with Stage III disease warrants further investigation.

<table>
<thead>
<tr>
<th>Guideline – Non-small Cell Lung Cancer – When to Avoid Radiotherapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative radiotherapy in patients with completely resected Stage I or II NSCLC is not recommended because of its detrimental effect on survival.</td>
<td>1</td>
<td>55</td>
</tr>
</tbody>
</table>
COMPLICATIONS OF THORACIC RADIOTHERAPY

Acute side effects of thoracic radiotherapy include anorexia, fatigue and oesophagitis. Oesophagitis is more severe and prolonged in patients treated with accelerated radiotherapy. Delayed side effects include pneumonitis and lung fibrosis. The risk of pneumonitis increases with dose and the volume of lung irradiated. The magnitude of these two risk factors can be expressed as a single quantity, either as the mean lung dose, or as the percentage of lung receiving a specified minimum dose derived from dose-volume histogram analysis, to predict the probability of a patient developing serious pneumonitis. Much more information correlating risk of pneumonitis with the mean lung dose or the V_{20} (volume of lung receiving 20Gy or more) is required, however, in one single institution series, fatal pneumonitis was not observed if the V_{20} was less than 32%.

Spinal cord injury is a potential complication of thoracic radiotherapy, but rarely seen if the dose is under 50Gy using conventional 2Gy fractions. Schultheiss has estimated the risks to be 0.2% after 45Gy and 1–5% at five years after 60Gy with conventional fractionation.

5.4 CHEMOTHERAPY AND ADJUVANT OR NEO-ADJUVANT TREATMENT OF LOCOREGIONAL NON-SMALL CELL LUNG CANCER

SURGERY AND ADJUVANT CHEMOTHERAPY

The strongest evidence regarding the role of postsurgical adjuvant chemotherapy is derived from the meta-analysis of randomised trials comparing adjuvant chemotherapy to no adjuvant chemotherapy carried out by the Non-Small Cell Lung Cancer Collaborative Group.

Patients who received adjuvant chemotherapy in five trials using non-platinum based regimens had worse survival. There was a 15% increase in the relative risk of death (p=0.005) with an absolute reduction in survival of 4% at two years and 5% at five years. These regimens are alkylating agent-based and are no longer used in clinical practice.

In eight trials investigating platinum-based regimens, there was a 13% decrease in the relative risk of death with adjuvant chemotherapy (p=0.08). Absolute survival was improved by 3% at two years and 5% at five years. These differences were not statistically significant.
The meta-analysis also addressed the question of the role of combined chemotherapy and radiotherapy given in the adjuvant setting. Four trials compared adjuvant chemoradiation versus adjuvant irradiation alone. For cisplatin-based combination chemotherapy there was a 6% decrease in the relative risk of death (p=0.46). Absolute survival was increased with chemotherapy by 2% at two years and 2% at five years. These differences were not statistically significant.  

<table>
<thead>
<tr>
<th>Guideline – Non-small Cell Lung Cancer – Adjuvant Therapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>The administration of adjuvant platinum-based chemotherapy is not recommended following surgery because it has not been definitively shown to significantly improve survival.</td>
<td>1</td>
<td>35</td>
</tr>
</tbody>
</table>

**SURGERY AND NEO-ADJUVANT CHEMOTHERAPY**

Under this section, studies were included where patients planned for surgical resection were randomised to receive chemotherapy or no chemotherapy prior to surgery (with or without radiotherapy). A list of these trials is given in Table 3–5. Evidence for the benefit of neo-adjuvant cisplatin-based chemotherapy comes from the two fully published trials, for which long-term follow-up has recently been published. Four other studies using cisplatin-based chemotherapy and one using single agent docetaxel were inconclusive.

In the study from Roth et al, 60 patients with Stage IIIA NSCLC were randomised to surgery alone (32 patients), or surgery preceded by three cycles of cisplatin, etoposide and cyclophosphamide (28 patients). Postoperative radiotherapy was given to patients with unresectable disease, or if the resection had been incomplete. The trial was stopped after a single unplanned interim analysis due to significantly improved median survival in the chemotherapy arm, 64 months versus 11 months (p<0.008).

An update of this study, with median follow-up of 82 months, has recently been reported. Median survival was 21 months in the perioperative chemotherapy arm and 14 months in the surgery-alone arm (p=0.056 log rank test, p=0.048 Breslow-Gehan-Wilcoxon test). The overall three- and five-year survival was 43% and 36% respectively for the chemotherapy arm, and 19% and 15% for the surgery-alone arm.
In the second fully reported study, from Rosell et al, 60 patients with Stage IIIA NSCLC were randomised to surgery, or surgery preceded by three cycles of mitomycin C, ifosfamide and cisplatin\textsuperscript{51,60}. All patients received thoracic irradiation after surgery. Interim analyses were planned for 12, 18 and 24 months from the start of the study. Accrual was stopped after 24 months when a significant median survival difference in favour of the chemotherapy arm became apparent, 20 months versus 5 months, (\textit{p}<0.001). A recent seven-year update of the results of this study showed that median survival was 22 months for the chemotherapy group and 10 months for the surgery-alone group (\textit{p}=0.005 log rank test)\textsuperscript{60}. Three- and five-year survival rates were 20\% and 17\% respectively for the chemotherapy arm, compared with 5\% and 0\% for the surgery-alone arm.

Further studies are required to establish the categories of Stage IIIA patients for whom the neo-adjuvant chemotherapy followed by surgery is appropriate, and to clarify its efficacy relative to non-surgical interventions.

<table>
<thead>
<tr>
<th>Guideline – Lung Cancer – Neo-adjuvant Therapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>For Stage IIIA patients managed surgically, platinum-based combination chemotherapy should be given prior to surgery as it improves survival. Neo-adjuvant chemotherapy may be beneficial in earlier stage disease, but the evidence is currently insufficient to support routine use (see Table 3–5).</td>
<td>II</td>
<td>51,52, 59,60</td>
</tr>
</tbody>
</table>
Table 3–5  Trials of surgery with or without preoperative chemotherapy in Stage IIIA non-small cell lung cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Stage</th>
<th>No (patients)</th>
<th>Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pass 1992</td>
<td>Stage III (N2)</td>
<td>27</td>
<td>CT + S + CT vs S + RT</td>
<td>Median survival CT/S 29 months vs S 16 months (p = 0.095).</td>
</tr>
<tr>
<td>Roth 1994</td>
<td>Stage IIIA</td>
<td>60</td>
<td>CT + S +/- CT vs S +/- RT (CEP)</td>
<td>Trial stopped at unplanned interim analysis.</td>
</tr>
<tr>
<td>Roth 1998</td>
<td></td>
<td></td>
<td></td>
<td>Median survival superior in CT arm, 21 months vs 14 months (p = 0.05).</td>
</tr>
<tr>
<td>Rosell 1994</td>
<td>Stage IIIA</td>
<td>60</td>
<td>CT + S + RT vs S + RT (MIC)</td>
<td>5-year survival superior in the CT arm, 36% vs 15%.</td>
</tr>
<tr>
<td>Rosell 1999</td>
<td></td>
<td></td>
<td></td>
<td>Trial stopped at planned interim analysis.</td>
</tr>
<tr>
<td>Depierre 1999</td>
<td>Stage IB–IIIA</td>
<td>373</td>
<td>CT + S +/- CT vs S (MIC)</td>
<td>Median survival superior in CT arm, 37 months vs 26 months (p = 0.09).</td>
</tr>
<tr>
<td></td>
<td>Stage IIIA</td>
<td>167</td>
<td></td>
<td>On multivariate analysis, relative risk of death for CT arm 0.77 (p = 0.05).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Perioperative mortality non-significantly increased in CT arm.</td>
</tr>
<tr>
<td>Mattson 2000</td>
<td>Stage IIIA</td>
<td>274</td>
<td>CT + RT vs RT or CT + S vs S (docetaxel)</td>
<td>Median survival superior in CT arm, 15 months vs 13 months (ns).</td>
</tr>
<tr>
<td>Elias 1997</td>
<td>Stage IIIA (N2)</td>
<td>47</td>
<td>CT + S + CT + RT vs RT+S+RT (PE)</td>
<td>Median survival CT/S 19 months RT/S 23 months (ns).</td>
</tr>
<tr>
<td>Ichinose 2000</td>
<td>Stage IIIA (N2)</td>
<td>62</td>
<td>CT + S vs S (PV)</td>
<td>Median survival CT/S 18 months S 16 months (p = 0.6).</td>
</tr>
</tbody>
</table>

* = reference

CT chemotherapy; S surgery; RT radiotherapy; CEP cyclophosphamide, etoposide, cisplatin; MIC mitomycin, ifosfamide, cisplatin; PE cisplatin, etoposide; PV cisplatin vindesine; ns non-significant
5.5 CHEMOTHERAPY IN ADVANCED/METASTATIC NON-SMALL CELL LUNG CANCER

GENERAL ASPECTS

Patients with advanced/metastatic NSCLC consist of those patients whose disease is either:
- Stage IV (distant metastases) at the time of diagnosis of NSCLC
- Stage IV (distant metastases) developing after treatment for earlier stage NSCLC
- recurrent local intrathoracic disease after treatment for NSCLC
- unresectable Stage IIIIB with disease beyond suitability for radical irradiation (for example, pleural effusion).

There are a group of patients who present with earlier stage NSCLC, but who are not able to receive surgical or radical irradiation because of major comorbidity or other factors. While the management of such patients has elements in common with the management of advanced NSCLC, they are not usually included with advanced NSCLC patients in clinical trials, particularly trials of systemic therapies.

The aim of treatment of advanced NSCLC is palliative. The palliative management of advanced NSCLC may involve treatment by oncologists, respiratory medicine physicians, palliative care physicians, and occasionally other medical specialists. The active participation of the patient’s general practitioner is very important.

The specific goals of treating advanced NSCLC are to:
- extend the patient’s life
- relieve the patient’s symptoms
- improve the patient’s quality of life.

When evaluating clinical trials, the important endpoints are therefore survival, changes in symptoms, and changes in quality of life. The response rate to a treatment, while often the primary endpoint of phase II trials, is not of comparable interest.

The management of symptoms from metastatic NSCLC is covered elsewhere in these guidelines (refer to Chapters 7 and 8). Some sites of disease (for example, brain metastases with cerebral oedema, vertebral metastases with spinal cord compression) and syndromes (for example, malignant hypercalcaemia) are better palliated with non-chemotherapy treatments (for example, radiation therapy, bisphosphonates). Chemotherapy should not therefore be used as the primary treatment for these problems.
THE ROLE OF SYSTEMIC CHEMOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER

Three meta-analyses have been published examining the influence of chemotherapy on survival in advanced/metastatic NSCLC. The Non-Small Cell Lung Cancer Collaborative Group meta-analysis was of 11 randomised controlled trials involving 1,190 patients randomised to either chemotherapy or no chemotherapy. The other two meta-analyses were smaller (six and seven trials respectively) and all trials analysed by these groups were included in the Non-Small Cell Lung Cancer Collaborative Group meta-analysis. Therefore this analysis, which was based on individual patient data, is the most comprehensive.

Chemotherapy provided a modest but highly statistically significant improvement in survival over supportive care alone. Statistical heterogeneity was apparent concerning the type of chemotherapy, such that a detrimental effect was observed for the two trials that used long-term administration of alkylating agent chemotherapy, no effect was seen in one trial that used vinca alkaloid/etoposide chemotherapy, and significant benefit was seen for the seven trials that used cisplatin-based chemotherapy. In the cisplatin chemotherapy trials (totalling 778 patients), the hazard ratio for death at one year was 0.73 (CI 0.63–0.85), corresponding to an absolute improvement in one-year survival from 16% to 26% and an improvement in median survival from 4.0 months to 5.5 months. For all chemotherapy trials (1190 patients), the hazard ratio for death at one year was 0.84 (CI 0.74–0.95).

This meta-analysis examined the influence of disease extent on the beneficial effect of cisplatin-based chemotherapy, analysing the following: metastatic versus non-metastatic, histological subtype (squamous versus adenocarcinoma versus other), performance status (‘good’ versus ‘poor’), age, and sex. All subgroups were found to derive benefit from treatment.

Data on relief of symptoms and changes in quality of life were not uniformly collected in the trials that were combined in these meta-analyses, and no analysis of these endpoints was performed.

Since the publication of the Non-Small Cell Lung Cancer Collaborative Group meta-analysis, six other trials have been reported where patients were randomly allocated to treatment with chemotherapy or to not receive chemotherapy. Cullen et al. used a combination of cisplatin, ifosfamide and mitomycin C in a trial of 351 patients with metastatic NSCLC. There was a significant prolongation of median survival (6.7 months versus 4.8 months, p=0.03) with chemotherapy. Quality of life was assessed in a subset of patients only, and showed an improvement over the first six weeks with chemotherapy, whereas it progressively declined in the no-chemotherapy patients. A study from Thailand randomised 287 patients to either cisplatin; ifosfamide and epirubicin chemotherapy; cisplatin/mitomycin C/vinblastine chemotherapy or no chemotherapy. Survival was significantly prolonged in both chemotherapy arms, and quality of life (using modified, translated ‘Western’ scales) was significantly improved with chemotherapy.
The other four trials compared single agent chemotherapy using one of the newer cytotoxic agents introduced in the 1980s and 1990s (hereafter referred to ‘new’ agents)\textsuperscript{71,72,73,74}. These trials are summarised in Table 4–5. Significant beneficial effects were found on survival and/or symptom control and quality of life in all studies. Patients with performance status of greater than 2 (see Appendix 3) or with other major co-existing medical problems were generally excluded from clinical trials.

Many other clinical factors have been shown to be markers of poor prognosis in advanced NSCLC patients\textsuperscript{75}. However, there is no evidence that benefit experienced from chemotherapy is confined to particular patient subgroups. In particular, both a meta-analysis and a large randomised trial did not identify extent of metastatic disease, histological subtype, age, or sex as predictors of benefit\textsuperscript{35,69}. Only one trial has specifically enrolled only elderly (age \(\geq 70\) years) patients\textsuperscript{74}. This trial showed significant prolongation of survival with single-agent vinorelbine chemotherapy compared to supportive care.

Table 4–5 \textit{Randomised trials of ‘new’ agents versus supportive care}

<table>
<thead>
<tr>
<th>Study agent</th>
<th>Patients</th>
<th>Survival</th>
<th>Quality of life</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>157</td>
<td>Significantly improved</td>
<td>No significant difference</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>300</td>
<td>No significant difference</td>
<td>Better QOL and better symptom control with</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>gemcitabine</td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>207</td>
<td>Significantly improved</td>
<td>Better QOL and better symptom control with</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with docetaxel</td>
<td>docetaxel</td>
<td></td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>191*</td>
<td>Significantly improved</td>
<td>Better QOL and better symptom control with</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with vinorelbine</td>
<td>vinorelbine</td>
<td></td>
</tr>
</tbody>
</table>

* trial restricted to patients aged \(\geq 70\) years. QOL – quality of life
Chemotherapy is appropriate treatment for patients with advanced NSCLC who have good performance status (ECOG ≤ 2) and are otherwise medically fit as it has been shown to improve survival.

Chemotherapy can result in beneficial effects on symptoms and quality of life in patients with advanced NSCLC.

**APPROPRIATE CHEMOTHERAPY FOR TREATING ADVANCED NON-SMALL CELL LUNG CANCER**

**SINGLE AGENT VERSUS COMBINATION CHEMOTHERAPY**

The evidence for benefit from cisplatin-based chemotherapy on survival was derived from trials where cisplatin was combined with older drugs including vinca alkaloids (vindesine, vinblastine), etoposide, doxorubicin, cyclophosphamide and mitomycin C. Another meta-analysis (using only published trials, without individual patient data) has examined the effect on response rates, survival and toxicity of combination chemotherapy compared to single-agent chemotherapy. Combination chemotherapy produced a significantly higher response rate, significantly better six- and 12-month survival and higher levels of toxicity. However, benefit on survival was not apparent when only trials that had cisplatin or vinorelbine as the single-agent arm were considered, suggesting that the overall benefit was attributable to older trials where the single-agent arm was ineffective. Further studies are required to better define the role of single-agent therapy with the ‘new’ agents compared to combination chemotherapy. This is particularly important for patients with performance status 2, who may not tolerate combination chemotherapy, as well as for better performance status patients.

Several more recent trials have compared the combination of a ‘new’ drug plus cisplatin with cisplatin alone. These are summarised in Table 5–5. All trials except one have shown significantly improved survival with the combination.
Table 5–5  Randomised trials of ‘new’ agents plus cisplatin versus cisplatin

<table>
<thead>
<tr>
<th>New agent</th>
<th>Patients</th>
<th>Survival</th>
<th>Quality of life</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>414</td>
<td>No significant difference</td>
<td>No significant difference</td>
<td>77</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>432</td>
<td>Significant survival advantage with combination</td>
<td>Not assessed</td>
<td>78</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>552</td>
<td>Significant survival advantage with combination</td>
<td>No significant difference</td>
<td>79</td>
</tr>
<tr>
<td>Tirapazamine</td>
<td>446</td>
<td>Significant survival advantage with combination</td>
<td>No significant difference</td>
<td>80</td>
</tr>
</tbody>
</table>

One phase III trial of 169 patients has compared single agent gemcitabine to the combination of cisplatin and vindesine. Survival and control of symptoms were equivalent, but quality of life improved in more patients in the gemcitabine arm\(^{81,82}\). Two smaller trials have compared single agent gemcitabine to the combination of cisplatin and etoposide\(^{83,84}\). With short follow-up, both trials reported no difference in response rate or survival. As expected, in all these trials, the cisplatin arms had more severe toxicity than single-agent therapy. None of these trials is large enough to be adequately powered to exclude inferior survival with gemcitabine compared to the combination therapy.

**Guidelines – Non-small Cell Lung Cancer – Combination Chemotherapy**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination chemotherapy is preferable to single agent therapy in patients with advanced NSCLC.</td>
<td>I</td>
<td>76</td>
</tr>
<tr>
<td>For patients where combination chemotherapy is contraindicated, single agent therapy with one of the ‘new’ agents (either a taxane, gemcitabine or vinorelbine) is appropriate.</td>
<td>II</td>
<td>83,84</td>
</tr>
</tbody>
</table>
`NEW' VERSUS 'OLD' COMBINATIONS WITH PLATINUM

A series of trials have compared ‘old’ platinum combinations (for example, cisplatin plus vinca alkaloid, cisplatin plus etoposide/teniposide) to ‘new’ platinum combinations. The ‘new’ combinations tested include cisplatin combined with paclitaxel\(^{85,86}\), vinorelbine\(^{87}\), gemcitabine\(^{88,89}\), tirapazamine\(^{90}\) and irinotecan\(^{91}\). In some studies there was a modest survival benefit for the new regimen\(^{85,87}\) and in others improved quality of life\(^{86}\). In the remainder, survival and quality of life outcomes were similar in both arms.

CISPLATIN VERSUS CARBOPLATIN TRIALS

Combination chemotherapy regimens using either cisplatin or cisplatin replaced by carboplatin have been directly compared in three phase III trials\(^{92,93,94}\). There was no consistent evidence of the superiority of one drug over the other. Emesis and renal toxicity were greater with cisplatin whereas haematological toxicity was greater with carboplatin.

TRIALS COMPARING ‘NEW’ DRUG PLUS PLATINUM COMBINATIONS

Many trials have been performed in the last five years comparing various ‘new’ regimens. The large majority of these have been published only in abstract form. The results of some of the largest trials are summarised in Table 6–5.

The largest trial\(^{95}\) was conducted by the Eastern Cooperative Oncology Group (ECOG) in the US. Over 1,200 patients were randomised to the control arm of paclitaxel over 24 hours plus cisplatin\(^{85}\) or one of three other regimens. Response rate and overall survival times were not significantly higher in any of the three experimental arms. A marginal but statistically significant benefit in time to progression was found in the cisplatin/gemcitabine arm, however, the chemotherapy in this arm was administered every four weeks, rather than every three weeks as in the control arm, making assessment of this endpoint difficult. Toxicity was variable, but less acute emesis and febrile neutropenia occurred in the carboplatin/paclitaxel arm. The inconvenience of the 24-hour paclitaxel infusion makes this regimen less suited to the palliative setting. While no significant disadvantage occurred with cisplatin/docetaxel, the activity of docetaxel in second-line therapy (see below) indicates alternative drugs may be preferable for first-line therapy.

The above ECOG trial was originally intended to enrol patients with performance status 0,1 or 2 but a high rate of toxicity resulted in termination of accrual of performance status 2 patients. Most other trials in Table 6–5 have been restricted to performance status 0 or 1 patients.
Two trials have evaluated the addition of a third ‘new’ agent to a new drug plus platinum combination\(^{96,97}\). In one trial\(^{96}\) the initial report has shown significant benefit to the triplet combination. Other trials examining various triplet combinations are being conducted.

**Table 6–5  Randomised trials of ‘new’ agents**

<table>
<thead>
<tr>
<th>Design</th>
<th>Patients</th>
<th>Outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>cisplatin/paclitaxel vs cisplatin/gemcitabine</td>
<td>1207</td>
<td>Survival and response rates equivalent. Longer time to progression with cisplatin/gemcitabine. Less nausea and febrile neutropenia with carboplatin/paclitaxel.</td>
<td>95</td>
</tr>
<tr>
<td>cisplatin/docetaxel vs carboplatin/paclitaxel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cisplatin/gemcitabine vs cisplatin/gemcitabine/paclitaxel</td>
<td>371</td>
<td>Triplet arms had superior survival and longer time to worsening symptoms.</td>
<td>96</td>
</tr>
<tr>
<td>cisplatin/gemcitabine/vinorelbine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paclitaxel/carboplatin vs paclitaxel/gemcitabine</td>
<td>329</td>
<td>Equivalent response rate, survival and toxicity.</td>
<td>98</td>
</tr>
<tr>
<td>paclitaxel/carboplatin vs cisplatin/vinorelbine</td>
<td>444</td>
<td>Equivalent survival and QOL. Less haematological toxicity and emesis with carboplatin/paclitaxel.</td>
<td>99</td>
</tr>
<tr>
<td>docetaxel/cisplatin vs docetaxel/gemcitabine</td>
<td>414</td>
<td>Equivalent response rate and survival. More diarrhoea with docetaxel/cisplatin. Both arms received G-CSF support.</td>
<td>100</td>
</tr>
<tr>
<td>gemcitabine/cisplatin vs vinorelbine/cisplatin</td>
<td>180</td>
<td>Cisplatin/vinorelbine closed at interim analysis because of worse survival. Accrual continues to other arms.</td>
<td>97</td>
</tr>
<tr>
<td>gemcitabine/cisplatin/vinorelbine/gemcitabine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gemcitabine/vinorelbine vs vinorelbine</td>
<td>120*</td>
<td>Closed at interim analysis because of survival benefit with combination. Longer time to symptom and QOL deterioration with combination.</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Trial restricted to patients aged ≥70 years

QOL = quality of life; G-CSF = granulocyte colony stimulating factors

Other platinum-ased combinations such as carboplatin plus gemcitabine or carboplatin plus vinorelbine have been investigated in phase II trials and have shown some activity, but phase III data to support their use is lacking.
NON-PLATINUM NEW DRUG COMBINATIONS

Two phase III trials have compared the combination of two new drugs with a platinum plus one new drug combination\textsuperscript{98,100} (Table 6–5). Neither trial showed any benefit of the non-platinum arm in terms of response rate or survival. Both trials failed to show a marked reduction in toxicity with the omission of platinum.

One trial restricted to elderly patients compared the combination of gemcitabine and vinorelbine to vinorelbine alone\textsuperscript{101}. This trial was closed with accrual of only 120 patients because an interim analysis showed a significant benefit with the combination. The results obtained with the vinorelbine alone arm in this trial appear substantially worse than the previous trial performed by this group\textsuperscript{74}.

<table>
<thead>
<tr>
<th>Guidelines – Non-small Cell Lung Cancer – Choice of Chemotherapy Agents</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the present time, no one chemotherapy regimen can be recommended over another. Based on currently available trial results, various combinations of a platinum drug plus a ‘new’ agent are reasonable options for performance status 0 or 1 patients. The use of combinations of three or more drugs, and the use of non-platinum combinations require further investigation before incorporation into standard practice.</td>
<td>II</td>
<td>85,86,87,88</td>
</tr>
<tr>
<td>Carboplatin can be used instead of cisplatin in combination chemotherapy.</td>
<td>II</td>
<td>92,93,94</td>
</tr>
</tbody>
</table>

APPROPRIATE DOSE AND DURATION OF CHEMOTHERAPY

The clinical trials evaluating various cytotoxics in NSCLC have used doses derived from phase I and II studies where routine use of colony-stimulating factor support, stem-cell support or use of cytoprotectants such as amifostine was not permitted. Only a small number of trials have specifically addressed cytotoxic doses in NSCLC patients. Two trials evaluating higher doses of paclitaxel\textsuperscript{85,102} have shown no survival benefit for the higher dose. Increased frequency\textsuperscript{103} or dose of cisplatin\textsuperscript{101} have not been shown to be more effective than four weekly administration or lower doses (50 mg/m\textsuperscript{2}) respectively.

In most of the discussed clinical trials in advanced NSCLC, treatment was generally administered for up to six to nine cycles in the absence of disease progression or severe toxicity. The cumulative non-haematological toxicity seen with agents such as platinum, paclitaxel, docetaxel and vinorelbine makes prolonged administration unfeasible. In trials where symptom control has been assessed in detail, improvement with chemotherapy is apparent within two to three cycles, and correlates with response or non-progression on radiological assessments.
Two recent trials have addressed the duration of chemotherapy. One trial\textsuperscript{105} compared the administration of three or six cycles of the older cisplatin/vinblastine/mitomycin C combination, and reported that there were no differences in survival or symptom relief between the schedules. A second trial\textsuperscript{106} used the more currently accepted combination of carboplatin and paclitaxel. Patients were randomised to receive four cycles or to continue to receive treatment until documented disease progression. No difference in survival was reported, and as expected the continuous arm had an increasing incidence of peripheral neuropathy. Neither of these trials directly randomised only responding patients to continue or cease treatment, although a retrospective analysis of the data from the first trial suggests that stopping therapy is not detrimental to these patients\textsuperscript{106}.

As only a minority of advanced NSCLC patients will show significant reduction of tumour mass with chemotherapy, it is particularly necessary to take care to avoid continuation of ineffective therapy.

<table>
<thead>
<tr>
<th>Guidelines – Non-Small Cell Lung Cancer – Chemotherapy Doses and Cycles</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is no indication to use greater than standard doses or dose intensity of chemotherapy in advanced NSCLC.</td>
<td>II</td>
<td>85,102, 103,104</td>
</tr>
<tr>
<td>Continuing multi-agent platinum-based chemotherapy beyond three to four cycles does not provide additional survival benefit.</td>
<td>II</td>
<td>105,106</td>
</tr>
<tr>
<td>Patients receiving chemotherapy for advanced NSCLC should be evaluated for effectiveness of treatment after two to three cycles. Treatment should be discontinued if no benefit is seen.</td>
<td>IV</td>
<td>106</td>
</tr>
</tbody>
</table>

**THE ROLE OF SECOND-LINE CHEMOTHERAPY AND OTHER AGENTS IN ADVANCED NON-SMALL CELL LUNG CANCER**

Most studies in which the use of second-line chemotherapy at the time of progression or relapse has been evaluated are phase II trials\textsuperscript{107}. These involve small numbers of patients and little information is provided on the performance status and the extent and nature of prior treatment of the patients. The rate of response to treatment is often the major endpoint assessed and the trial designs do not allow for any reliable assessment of patient benefit to be made.

Two randomised phase III studies of docetaxel in patients previously treated with cisplatin-based chemotherapy are available. Both showed a survival advantage: one compared docetaxel with best supportive care\textsuperscript{108} and the other compared docetaxel with vinorelbine or cyclophosphamide\textsuperscript{109}.
BIOLOGICAL AGENTS

The role of biological agents in NSCLC is an emerging area of research. Numerous compounds are in various phases of preclinical and clinical development. A promising group of small molecules are inhibitors of the epidermal growth-factor tyrosine kinase. Early phase studies suggest that symptom improvement can occur with the use of these compounds. However, further research is required before these compounds have an established place in lung cancer management.

<table>
<thead>
<tr>
<th>Guideline – Non-small Cell Lung Cancer – Second Line Chemotherapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>In selected good performance status patients, second-line chemotherapy with docetaxel may be considered.</td>
<td>II</td>
<td>108,109</td>
</tr>
</tbody>
</table>

References


93. Jelic S, Radosavjelic D, Elezar E, et al. Survival advantage for carboplatin 500 mg/m2 substituting cisplatin 120mg/m2 in combination with vindesine and mitomycin C in patients with stage IIIIB and IV squamous cell bronchogenic carcinoma: a randomised study in 221 patients. Lung Cancer 18 (S1)[14]. 1997.


6. **SMALL CELL LUNG CANCER**

6.1 Management of small cell lung cancer by stage

6.2 Chemotherapy and small cell lung cancer
   - OCA and PE
   - Alternating regimens
   - Carboplatin versus cisplatin
   - Oral etoposide
   - Other regimens
   - Maintenance therapy
   - The optimum chemotherapy regimen
   - Appropriate duration of chemotherapy
   - Appropriate number of cycles of chemotherapy
   - Dose escalation of chemotherapy
   - Second-line chemotherapy
     - Optimum second-line chemotherapy regimen

6.3 Radiotherapy
   - Chest radiotherapy in limited stage small cell lung cancer
   - Prophylactic cranial irradiation
   - Other indications for thoracic radiotherapy
6.1 MANAGEMENT OF SMALL CELL LUNG CANCER BY STAGE

Table 6-1 Management of small cell lung cancer stage by stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Optimal management</th>
<th>If patient is not suitable for optimal management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited Disease</td>
<td>Platinum based chemotherapy (4–6 cycles) combined with thoracic radiotherapy</td>
<td>Palliative chemotherapy +/− radiotherapy</td>
</tr>
<tr>
<td></td>
<td>concomitant with first or second cycle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prophylactic cranial irradiation for complete responders</td>
<td></td>
</tr>
<tr>
<td>Extensive Disease</td>
<td>Combination chemotherapy (4–6 cycles)</td>
<td>Symptom control</td>
</tr>
<tr>
<td></td>
<td>Prophylactic cranial irradiation for complete responders</td>
<td></td>
</tr>
</tbody>
</table>

6.2 CHEMOTHERAPY AND SMALL CELL LUNG CANCER

The recognition during the 1970s that SCLC is a systemic disease, best treated with chemotherapy, led to the relegation of radiotherapy to a secondary role in its management. Chemotherapy is associated with high response rates, but most patients subsequently relapse, and the efficacy of available cytotoxic drugs appears to have plateaued. Furthermore, observations in patients treated with chemotherapy alone revealed that the primary site, where the disease was usually bulkiest, and the brain, which is a chemotherapy sanctuary site, were common sites of treatment failure. Multimodality strategies designed to address these problems has resulted in a re-emergence of radiotherapy, particularly in the management of limited disease. As a result, about a quarter of patients with limited disease can now be cured with a combination of chemotherapy and radiotherapy, but the majority of patients who present with extensive disease will nearly all succumb to it.

OCA AND PE

The two most widely used regimens have been vincristine, adriamycin and cyclophosphamide (known variously as OCA, VAC, or CAV) and, more recently, cisplatin with etoposide (PE). Median survival of 12–18 months in limited stage and 7–12 months in extensive stage SCLC have been routinely reported with either of these regimens. An analysis of results through the 1970s and 1980s for the control arms of 21 randomised phase III trials in extensive disease showed a modest improvement in median survival from 7.0 months, for patients enrolled between 1972 and 1981, to 8.9 months for the 1982–90 cohort.1
Impressive results have been achieved with four cycles of PE in a recent study. Four hundred and nineteen patients with limited stage disease received identical chemotherapy but were randomised to differing schedules of thoracic radiotherapy. Two-year survival was 41% and five-year survival 16% for once daily therapy, while twice daily therapy was better, yielding 47% survival at two years and 26% at five years.

A number of studies have compared outcomes with OCA and PE. Larger trials have included a study from the Southeastern Cancer Study Group, where 437 patients with extensive stage disease were randomised to 12 weeks of PE, or 18 weeks of either OCA or OCA/PE alternating. There was no difference in response or survival between the PE and OCA arms. In a South Western Oncology Group (USA) (SWOG) study, 400 limited stage patients were randomised to a platinum-containing arm of alternating PE and OCA, versus etoposide, vincristine, adriamycin and cyclophosphamide. Median survival was 15–16 months and was not different between the arms. In a study from Fukuoka, 288 patients with limited or extensive stage disease were randomised to PE, OCA, or an alternating regimen. Patients also received radiotherapy. Response rates were 78% with PE and 55% with OCA. There was no difference in survival between these two regimens, but there was significantly more toxicity (haematological and neurological) in the OCA arm.

Two meta-analyses have looked at randomised trials comparing platinum-containing and non-platinum regimens. The first, from Pujol, included 18 trials, with a total of 4 054 patients. Response rate was higher for cisplatin-containing regimens, with an odds ratio of 1.35 (p<0.00001). Survival favoured cisplatin-containing regimens, with six-month survival 68% versus 65% and 12-month survival 29% versus 24%. The odds ratio for survival was 0.87 at six months (p=0.03) and 0.80 at 12 months (p=0.002). Results were unaltered when considering only trials where both arms included etoposide.

The second meta-analysis included 36 trials, and focused on the role of etoposide as well as cisplatin. Only fully published trials were included. Overall survival benefit was shown for regimens containing cisplatin (OR 0.61, p<0.001) or etoposide (OR 0.65, p<0.001.) Nine trials, involving 1 945 patients, specifically compared a regimen containing both cisplatin and etoposide versus a regimen containing neither drug. The meta-analysis favoured the PE combination (OR 0.57, p<0.001).

Neither of the meta-analyses examined individual patient data, however, despite this limitation, there is clear benefit for regimens containing both cisplatin and etoposide. A further consideration for patients undergoing radiotherapy is the toxicity of the chemotherapy regimen in this context. OCA is associated with greater toxicity than PE when combined with radiotherapy. If radiotherapy is to be administered concurrently with chemotherapy then a combination of a platinum agent and etoposide is suggested.
ALTHERNATING REGIMENS

In an effort to improve results, alternating or sequential regimens, particularly of OCA and PE, have been used. Results have, for the most part, not shown an advantage for any particular approach. There were no significant differences in outcome in a trial of 437 patients with extensive disease randomised to 12 weeks of PE, 18 weeks of OCA or 18 weeks of alternating OCA/PE. In a phase III SWOG trial, 400 patients with limited stage disease were randomised to alternating PE/OCA or a combination of etoposide with OCA, with chest radiotherapy. There were no significant differences in response rate or survival. In a study from the National Cancer Institute of Canada, 300 patients with limited disease were randomised to three cycles of OCA followed sequentially by three cycles of PE, or alternation of the two regimens. There were no observed differences in patient outcome between the regimens. In a study of 129 patients, following initial therapy with four cycles of PE, responding patients were randomised to no further treatment or to consolidation with OCA. Survival was no different between the arms, but toxicity was increased in the consolidation group.

However, some studies have shown improved results with alternating regimens. Two hundred and eighty nine patients with extensive disease were randomised to receive OCA or OCA alternating with PE. Alternating therapy was associated with improved response rate and overall survival. Alternating PE/OCA was also superior to OCA in the trial from Fukuoka, but not significantly superior to PE alone. Positive results in these two trials may be interpreted as superiority of a platinum-containing regimen.

In summary, the evidence for alternating regimens is inconsistent. The superiority of alternating therapy has not been clearly demonstrated.

CARBOPLATIN VERSUS CISPLATIN

Carboplatin has been widely used in Australia to replace cisplatin in the PE regimen, although few trials have compared carboplatin and cisplatin regimens. In a study from Greece, patients were randomised to either cisplatin and etoposide, or carboplatin and etoposide. Patients could also receive radiotherapy. One hundred and forty three patients were included, 82 with limited disease. There was no difference in response rate or overall survival between the two arms. However, there was less toxicity (neutropenic sepsis, emesis, nausea and vomiting, neurotoxicity) in the carboplatin arm. Lassen has reported on 484 patients randomised to either cisplatin or carboplatin in combination with teniposide and vincristine. In addition, the regimen was alternated with one of three other regimens. There was no difference in response, survival or toxicity rates between the cisplatin and carboplatin arms.
ORAL ETOPOSIDE

Oral etoposide has been investigated as a potential effective, low-toxicity oral regimen for SCLC in randomised trials. Souhami and colleagues randomised 155 patients to six cycles of either oral etoposide (100mg bd x 5d) or alternating PE/OCA. The study was closed early due to toxicity. One-year survival was worse in the oral etoposide arm than the intravenous arm (9.8% versus 19.3% respectively, p<0.05), with median survival 4.8 months versus 5.9 months. With the exception of chemotherapy-induced emesis, symptom control and quality of life favoured the intravenous regimen. The UK Medical Research Council Lung Cancer Working Party trial was also stopped after interim analysis. Three hundred and thirty nine patients were randomised to oral etoposide (50mg bd for 10d), or either OCA or PE. Survival was inferior in the oral arm (OR 1.35, p=0.03), with median survival 130 days versus 183 days for the intravenous arm. Survival at six months was 35% and 49%, and at 12 months 11% and 13% for the oral and intravenous regimens respectively. The palliative benefits were similar for each of the arms. These data indicate that oral etoposide is inferior treatment to combination intravenous regimens in terms of survival, with no additional quality of life or symptom control benefit.

OTHER REGIMENS

The role of ifosfamide has been examined in a phase III study of 162 patients with extensive stage disease. Patients were randomised to receive PE or PE plus ifosfamide. Median survival was longer in the ifosfamide arm, 9.1 months versus 7.3 months, with 12 month survival of 36% versus 27% respectively. A smaller randomised trial of 92 patients including both limited and extensive disease showed no difference in response rates or survival when ifosfamide was added to cisplatin/etoposide. Trial JCOG 9511, investigating irinotecan (CPT-11), has been reported in abstract form only. One hundred and fifty four patients with extensive disease were randomised to receive either cisplatin/etoposide or cisplatin/irinotecan (PI). The trial was stopped at interim analysis. Response rate was 67% with PE and 89% with PI (p=0.013). Median survival was 287 days with PE and 390 days with PI (p=0.004). A confirmatory study is currently being undertaken.

MAINTENANCE THERAPY

A number of trials have examined the role of maintenance therapy in SCLC, generally without improvements in overall survival. Patients with limited or extensive stage disease received ifosfamide, etoposide and an anthracycline (doxorubicin or epirubicin). Responding patients (n=84) were randomised to maintenance etoposide and vindesine for 12 courses, or no further therapy. Progression-free survival was increased but survival was not significantly different. The ECOG 7593 trial has been reported in abstract form only. Patients with extensive stage disease received initially four cycles of cisplatin and etoposide. Those stable or responding were then randomised (n=227) to four additional cycles of topotecan or no further therapy. Progression-free survival was improved but overall survival and 12 month survival was no different.
THE OPTIMUM CHEMOTHERAPY REGIMEN

<table>
<thead>
<tr>
<th>Guidelines – Small Cell Lung Cancer – Platinum as Optimal Chemotherapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum containing regimens produce superior survival to that seen with other regimens.</td>
<td>I</td>
<td>6,7</td>
</tr>
<tr>
<td>For patients with limited disease, when used in conjunction with thoracic irradiation, there is no evidence that any combination is superior to the doublet of cisplatin and etoposide.</td>
<td>I</td>
<td>12,13</td>
</tr>
</tbody>
</table>

APPROPRIATE DURATION OF CHEMOTHERAPY

Studies have compared four to six cycles of chemotherapy versus longer treatment durations. In a study including both limited and extensive stage disease, 265 patients were randomised to six or 12 cycles of chemotherapy. Survival was not different between the arms\(^2\). Six hundred and ten patients, again of mixed stage, were randomised to receive either four or eight cycles of cyclophosphamide, etoposide, and vincristine. Time to progression was increased in the longer arm, but survival was no different as long as patients in the short arm received further chemotherapy at relapse\(^2\). Giaccone has reported on 434 patients of mixed stage, randomised to either five or 12 cycles of cyclophosphamide, adriamycin and etoposide. Again, time to progression was increased in the longer treatment arm, but survival was no different. There was increased toxicity in the longer chemotherapy group\(^2\).

A study from Turrisi et al, where patients received four cycles of PE, highlighted the outcomes that may be achieved with short duration chemotherapy. Two-year survival for 419 patients with limited stage disease was 41–47\%, and five-year survival was 16–26\%\(^2\).

APPROPRIATE NUMBER OF CYCLES OF CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Guideline – Small Cell Lung Cancer – Cycles of Chemotherapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four to six cycles of chemotherapy should be given.</td>
<td>II</td>
<td>2,21,22,23</td>
</tr>
</tbody>
</table>
DOSE ESCALATION OF CHEMOTHERAPY

In the 1970s, a clinical correlation was seen between chemotherapy dose and response, where patients received either cyclophosphamide 700mg/m² or 1 500mg/m², along with carmustine and methotrexate. Subsequent trials have generally failed to confirm these findings. A meta-analysis of 60 randomised trials from the 1970s and 1980s investigated the role of dose intensity for a range of regimens. The range of variation in dose intensity was narrow. In extensive disease, there was no significant correlation between dose-intensity and survival, and results for limited disease were not consistent across regimens.

Ihde compared standard-dose and high dose PE in 90 patients with extensive stage SCLC. High-dose PE was delivered during the first two cycles only. A 46% increase in dose intensity did not improve outcome. The dose-intense four drug CODE regimen (cisplatin, vincristine, Adriamycin, etoposide), given over nine weeks, was compared with an 18 week OCA/PE regimen in a trial where 220 patients with extensive disease were randomised. Dose intensity was doubled, while the total dose of drugs delivered was the same for both arms. There were excessive treatment-related deaths in the CODE arm, and there was no difference in survival. In a trial of similar design, CODE plus the cytokine G-CSF, was compared with alternating OCA/PE. Two hundred and twenty seven extensive stage disease patients were randomised and there was no difference in survival between the arms.

Positive results have been reported in a number of studies. In a small study of 63 patients with extensive stage disease, patients were randomised to receive CODE or CODE plus G-CSF. Dose intensity was increased in the G-CSF arm, with a significant improvement in survival, from 32 weeks to 59 weeks. In a large study, 300 patients with good or intermediate prognosis were randomised to receive V-ICE (vincristine, ifosfamide, cisplatin, etoposide) either every three or four weeks. Patients were further randomised to receive either GM-CSF or no cytokine. GM-CSF did not alter the incidence of febrile neutropenia or the survival rate. Patients in the more intensive chemotherapy arm had improved survival (p=0.0014), with two-year survival increased from 18% to 33%. In a similar design trial, 403 good prognosis patients were randomised to receive six cycles of Adriamycin, cyclophosphamide and etoposide (ACE) at either two or three week intervals. Patients in the two-week interval arm also received G-CSF. The received dose intensity was increased 34% in the two-week arm, and survival was improved from 39% to 47% at 12 months. Patients in the studies did not receive thoracic irradiation; similar results may have been obtained if radiation was included. Further studies are needed before a dose-intense approach may be considered to be standard therapy.
SECOND-LINE CHEMOTHERAPY

A frequent approach has been to treat with OCA on relapse following PE as first-line therapy, and vice versa. Where a good response was obtained with a first-line regimen, and the response was durable, 79% of patients responded to re-treatment with the same regimen in a small phase II study. The best results were obtained where there was a first-line complete remission and response duration was over eight months. There have been no randomised studies comparing this approach to use of an alternative regimen. Topotecan has been compared to OCA as second-line therapy in a randomised trial, where patients relapsed at least 60 days after primary chemotherapy. There was no significant difference in response rate, time to progression or survival. Symptom control (dyspnoea, fatigue, anorexia, hoarseness, interference with daily living) was superior in the topotecan group. A number of the other newer chemotherapy drugs have been shown to be efficacious for second-line therapy in SCLC, including paclitaxel and irinotecan.

OPTIMUM SECOND-LINE CHEMOTHERAPY REGIMEN

<table>
<thead>
<tr>
<th>Guidelines – Small Cell Lung Cancer – First and Second Line Chemotherapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Where a platinum agent and etoposide have been given first line, then appropriate second-line regimens include the combination of cyclophosphamide, adriamycin and vincristine, or single agent topotecan. These regimens are of similar efficacy.</td>
<td>II</td>
<td>33</td>
</tr>
<tr>
<td>If first line chemotherapy has produced a response which has gone beyond eight months duration, it is reasonable to trial the first line drug again.</td>
<td>III–3</td>
<td>32</td>
</tr>
</tbody>
</table>

6.3 RADIOTHERAPY

CHEST RADIOTHERAPY IN LIMITED STAGE SMALL CELL LUNG CANCER

There is strong evidence for the role of thoracic radiotherapy in patients having ‘radical’ treatment for SCLC. This topic has been reviewed in a number of randomised controlled trials and meta-analyses. Two meta-analyses were published in 1992 and both showed a benefit for thoracic radiotherapy. In the first analysis, the odds ratio for
benefit of radiotherapy on two-year survival was 1.52 (p<0.001) equating to a 5.4% increase in two-year survival. The addition of radiotherapy also improved local control by 25.3%, the odds ratio being 3.02 (p<0.0001). There was an excess of treatment related deaths in the combined treatment group with an odds ratio of 2.54 (p<0.01), but this only equated to a 1.2% difference in risk of treatment-related death. The second meta-analysis showed the same overall survival increase (5.4 ± 1.4%), but at three, not two years. The relative risk of death in the combined modality treatment group was 0.86 (p=0.001), corresponding to a 14% reduction in the mortality rate.

Most studies indicate additional benefit if the radiotherapy is given early rather than late, although in one randomised study (criticised for its methodology) there was no benefit for initial versus late chest irradiation. A second randomised study showed no clear benefit for concurrent over sequential treatment. The studies showing improved survival have generally used a total dose of at least 40Gy in 15Gy fractions over three weeks (or a biologically equivalent dose). Hyperfractionated thoracic radiotherapy has been shown in one large, fully published study to increase the long-term survival of patients with limited SCLC (five-year survival, 26% with hyperfractionated thoracic radiotherapy versus 16% with once daily radiotherapy). This was achieved with an increased rate of short-term Grade 3 esophagitis.

<table>
<thead>
<tr>
<th>Guidelines – Small Cell Lung Cancer – Chemotherapy and Radiotherapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with limited stage small cell lung cancer; the addition of thoracic radiotherapy to standard combination chemotherapy improves overall survival and should be incorporated into a comprehensive treatment plan.</td>
<td>I</td>
<td>35,36,37</td>
</tr>
<tr>
<td>Thoracic radiotherapy should be offered early in relation to the course of chemotherapy rather than late. Evidence supports the administration of chemotherapy concurrent with radiotherapy over sequential chemotherapy-radiotherapy administration.</td>
<td>II</td>
<td>2, 38, 39, 40, 41, 42, 43</td>
</tr>
<tr>
<td>Accelerated radiotherapy is associated with a survival advantage compared with standard fractionation.</td>
<td>II</td>
<td>2</td>
</tr>
</tbody>
</table>
PROPHYLACTIC CRANIAL IRRADIATION

There is strong evidence to recommend prophylactic cranial irradiation (PCI) for patients who have achieved complete remission following chemotherapy or chemoradiotherapy. Data from randomised controlled trials demonstrate that PCI decreases the frequency of brain metastases and increases disease free survival in these patients. An individual patient data meta-analysis of seven randomised trials showed a relative risk of death in the treatment group as compared to the control group of 0.84 (p=0.01), an increased rate of disease free survival relative risk of recurrence of 0.75 (p<0.001) and a decreased cumulative incidence of brain metastasis (RR 0.46, p<0.001). The cumulative incidence of brain metastasis at three years was 58.6% in the control group compared with 33.3% in the treatment group.

There may be a dose-response relationship in SCLC and a dose of 30Gy in 3Gy fractions or 36Gy in 2Gy fractions is recommended. In the study reported by Gregor, PCI delivered as a dose of 24Gy in 2Gy fractions was no better than no PCI, while 36Gy in 18Gy fractions significantly reduced CNS relapse. Other studies have shown this benefit with doses varying from 24Gy in 8Gy fractions to 40Gy in 20Gy fractions.

On the basis of non-randomised data, it is recommended that PCI be given as soon as possible after patients achieve complete remission. Suwinski et al noted a threshold in dose-response when PCI was delayed, consistent with rapid growth of untreated sub-clinical disease in SCLC.

There is evidence from randomised controlled trials with data for up to 30 months of follow-up that PCI does not produce significant late neurotoxicity. There is evidence from one randomised controlled trial that PCI does not have a detrimental effect on quality of life in the first 12 months following the completion of therapy. There is insufficient evidence to comment on the long-term effects of PCI on quality of life.

<table>
<thead>
<tr>
<th>Guideline – Small Cell Lung Cancer – Prophylactic Cranial Irradiation</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients who have achieved a complete response after induction therapy, prophylactic cranial irradiation is associated with a reduction in rate of brain metastases and prolongation of survival.</td>
<td>I</td>
<td>52</td>
</tr>
</tbody>
</table>
OTHER INDICATIONS FOR THORACIC RADIOTHERAPY

There is no evidence of any value in giving consolidation thoracic radiotherapy to patients with metastatic disease beyond the chest at presentation. The treatment from presentation onwards is palliative. The role of radiotherapy as a palliative modality conforms to palliation criteria in any disease entity or site.

Patients who are referred for consolidation thoracic radiotherapy after poor response to chemotherapy must have their histology reviewed as the first step in their management. If they are true SCLC, their prognosis is poor regardless of stage, with an expected median survival of two to three months only. Radiation therapy for these patients is palliative and is given when symptoms indicate.

References


SECTION IV
SYMPTOM CONTROL

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7.1 PALLIATIVE CARE FOR THE PERSON WITH LUNG CANCER

GENERAL

Hospice and palliative care has been defined as a concept of care that provides co-ordinated medical, nursing and allied services for people who are terminally ill, delivered where possible in the environment of the person’s choice, and which provides physical, psychological, emotional and spiritual support for patients and for patients’ families and friends. The provision of hospice and palliative care services includes grief and bereavement support for the family and other carers during the life of the patient and continuing after death\(^1\).

Palliative care utilises advanced planning rather than crisis intervention. It offers a multi-disciplinary model of care that is focused on the whole person within their social and emotional context, rather than just the disease. However, a good knowledge of the natural history of the disease and relevant oncological practice is essential for palliative care\(^2\).

Only one fifth of patients with lung cancer survive a year after diagnosis and have a significant burden of symptoms, emphasising the importance of palliative care in the management of the patient with lung cancer\(^3,4\). A palliative approach, involving attention to symptom control and the psychological, social and spiritual wellbeing of the patient and their family is relevant at all stages of the disease, and it has been argued that attention to these aspects combined with understanding of the patients’ feelings and concerns all contribute to improving quality of life of the person with lung cancer\(^4\).

Although focussing on quality of life, palliative care is also concerned with the quality of dying. Recent work by Christakis and co-workers\(^5\) has identified—by focus group work with health professionals, patients and carers—some attributes of a good death. The most important positive components were: good pain and symptom management, clear decision-making, preparation for death, completion, contributing to others, and affirmation of the whole person. Patients and families tended to fear ‘bad’ dying more than death itself. It was found that doctors had a biomedical emphasis with substantially different priorities to the other groups. Patients particularly valued continuing opportunities to make contributions of gifts, time and knowledge to those around them. Attributes of a ‘bad’ death included the lack of opportunity to plan ahead and arrange personal affairs, so as to decrease the burden on family, and to say goodbye.
SPECIALIST VERSUS GENERALIST PALLIATIVE CARE

Palliative care services have evolved in different ways, but in metropolitan areas specialist consultant palliative care services are generally available to give advice on symptom control and other problems, both in hospital and in the community. Access to hospice or specialist palliative care beds is also generally available. An evolving role is that of a specialist respiratory nurse to provide support for newly diagnosed cancer patients and palliative care6.

However, in rural and remote areas, this access is more limited. Consultations may be by telephone or video-conferencing and access to specialist inpatient care may be limited by distance.

The British Thoracic Society Lung Cancer Guidelines recommend that all hospital cancer units should consider holding sessions with a palliative medicine physician to ensure good liaison between the hospital and community7. This would also ensure optimum symptom control and early attention to psychological, emotional and social issues.

Most palliative care will be provided by the existing network of carers, co-ordinated by either the general practitioner or treating respiratory physician or oncologist, who in turn draws upon the expertise of other health professionals when particular issues arise. The National Strategy for Palliative Care encourages the use of existing networks and community services in conjunction with palliative care specialists to deliver palliative care8.

As the availability of specialist palliative care increases specialist palliative care teams should be utilised to achieve optimum outcomes for the patient with lung cancer, particularly when treating complex or difficult to resolve issues.

The involvement of a specialist palliative care team in the care of patients with cancer in general increases patient and carer satisfaction, increases the amount of time spent at home by patients, reduces the time spent in hospital, reduces the overall cost of care and increases the likelihood of the patient dying where they wish9.

<table>
<thead>
<tr>
<th>Guideline – Specialist Palliative Care Services</th>
<th>Level of Evidence</th>
<th>Refs</th>
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</thead>
<tbody>
<tr>
<td>Specialist palliative care services should be used to improve outcomes in the care of patients with cancer (lung cancer included).</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>
TIMING OF REFERRAL

Early referral to a palliative care service will usually be helpful and will be facilitated if the palliative care health professionals are already an integral part of the multidisciplinary treatment team at the cancer centre or treating hospital\textsuperscript{10,11}. Referral to a palliative care service should be based on need, not on life expectancy\textsuperscript{12}, but early referral to a palliative care team allows the establishment of access and contacts, and exploration of options for future care without the need for immediate decisions. Early referral will facilitate subsequent continuity of care between hospital, home and hospice, and thus mitigate against any sense of abandonment\textsuperscript{13,14,15}. General practitioners, who continue to be involved in the ongoing care of the patient, often initiate palliative care.

The concept of parallel care, suggesting a close and continuing co-operation between oncological and palliative services throughout the course of the illness, is particularly important for patients with lung cancer. The involvement of palliative care professionals does not preclude the continuation or commencement of chemotherapy, courses of radiotherapy, or other surgical or procedural interventions aimed at reducing tumour burden or relieving symptoms\textsuperscript{16}. However, the concurrent use of validated quality of life measurements, in conjunction with clinical trials looking at survival end-points, is particularly recommended in improving outcomes for patients with lung cancer\textsuperscript{4} (refer also to guideline in Chapter 4, p74).

SITES OF PALLIATIVE CARE

Palliative care emphasizes that care is delivered where possible in the environment of the patient’s choice. Good communication between health professionals is essential to ensure smooth transition from one site to another.

OWN RESIDENCE

This refers to either the patient’s own home, the home of another, a nursing home or hostel. Increasingly, staff in nursing homes and hostels are being called on to deliver palliative care where resources to care for a dying resident may be limited\textsuperscript{17,18}.

The general practitioner will be the key medical practitioner in delivering palliative care at home, usually with the assistance of community nurses. The local palliative care service will usually be able to add the support of specialist palliative care nurses and a specialist palliative care physician as well as counsellors, pastoral care workers and volunteers. Links with other community services mean that assistance can be accessed for physiotherapy, nutritional support, occupational therapy and home help\textsuperscript{8}.

It is essential that the patient and family have access to support 24 hours a day, seven days a week if unnecessary hospital admissions are to be avoided, and that they know who to call in the event of a crisis. Preference for home care may decrease during the course of the illness and hospital admission for terminal care be requested\textsuperscript{19}.
Although reliable data is limited, home care programs, where there is adequate support for the carers, are generally assessed favourably\textsuperscript{19,20,21,22}. Carers and relatives of terminally ill patients report more support was needed during care at home, particularly for activities of daily living and domestic chores\textsuperscript{23}. Families undertaking home care experienced higher levels of stress and social disruption than those whose relatives were cared for in institutions\textsuperscript{24}.

**ACUTE HOSPITAL**

Even when no further curative treatment is anticipated, situations arise which will be best treated in an acute hospital. These include orthopaedic management of a fracture or potential fracture, radiotherapy for a painful bone metastasis, superior vena caval obstruction or spinal cord compression, thoracentesis, treatment of hypercalcaemia or pain, and symptom control. A family caring for a patient at home may need respite for many reasons, and an acute hospital may be the only site available.

As the illness progresses and the patient's strength and time are limited, hospital outpatient visits for review may be burdensome and should be minimized by liaison between the hospital specialist, the local palliative care team and the general practitioner.

Where patients wish to continue their direct links with a specialist physician or hospital team, an effective level of contact should be achieved with priority based on patient need, preference and convenience.

Despite the availability of community based palliative care and hospices, many patients still die in acute care hospitals. Attention to symptom control, psychological and emotional support for the patient and family, and agreement on the goals of care can allow death to occur peacefully even in this setting.

It is vital that news of death in hospital be communicated to the general practitioner and community team as soon as possible, and suitable follow-up arranged.

**INPATIENT HOSPICES**

Admission for short periods may be required for symptom assessment and review of medication if new problems arise. Admission for respite may be required for family and patient relief. Direct admission from the acute hospital may be required where the patient is so functionally compromised and symptomatically burdened that they have needs that are unable to be provided in the community. This may be particularly so for patients suffering from severe dyspnoea associated with lung cancer. If the patient's condition improves or stabilises at an acceptable level, then discharge to home may be considered on a temporary or even day/weekend leave basis.
At times, although patients undertake the majority of their care at home, their wish may be for hospice care in the terminal phase to reduce the burden on family carers. This change in preference for hospice rather than home care highlights the importance of having adequate hospice beds available.

It is important to be clear who bears the primary responsibility for care in each setting. Continuity of care can be provided through clear communication between all health care providers and the patient and family, so that accurate and detailed information about all aspects of the patient’s condition, treatment and wishes is known.

**SYMPTOM MANAGEMENT**

Good symptom control is fundamental to the practice of oncology and is essential for supporting patients with progressive and advanced disease. Patients with advanced lung cancer experience more symptoms than patients with a range of other cancers including breast, colon and malignant melanoma. Although gradual resolution of distress is observed in most patients, high levels of physical symptoms and emotional distress persist in those with lung cancer, with declining physical abilities adversely affecting emotional wellbeing.

Physical symptoms most commonly reported are pain, dyspnoea, anorexia and fatigue, with cough, haemoptysis and insomnia also highlighted.

In a study of patients with poor prognosis SCLC and advanced NSCLC presenting for treatment, a multiplicity of symptoms (average 14–17 symptoms) were reported from a variety of domains. The commonest psychological symptoms were worry and anxious feelings, common constitutional symptoms were tiredness, lack of energy, lack of appetite and difficulty sleeping, while the most common chest symptoms were shortness of breath and cough. Overall the symptoms most frequently reported as severe were decreased sexual interest, lack of energy and shortness of breath.

In a prospective study of 100 consecutive lung cancer patients, 86% reported pain (moderate to severe in 70%), 70% had dyspnoea, 68% had anorexia, 52% reported constipation and 52% were easily fatigued. The median number of symptoms reported was nine. Patients with advanced lung cancer have the highest prevalence of dyspnoea of all cancer patients.

A study of 289 NSCLC patients reported cough (79%), dyspnoea (75%), malaise (47%) and anorexia (45%) as the most frequent symptoms on presentation. In this group of patients who were treated by surgery, radiotherapy or ‘best supportive care’, dyspnoea and cough were not as well palliated as pain and haemoptysis.

The presence of high symptom distress in newly diagnosed lung cancer patients is a predictor of reduced survival.
The principles of symptom control, which are used as standard by clinicians include:

• assessment of the symptom, including understanding the meaning ascribed to it by the patient
• explanation of the likely cause
• investigations should only be undertaken if they will change the course of action to be followed
• institution of treatment based on the known or likely aetiology, available options for treatment, and the wishes of the patient
• monitoring of the response to treatment and modification as necessary.


**KEY POINT:**

• **Patients with lung cancer experience a high incidence of physical symptoms including fatigue, pain, dyspnoea, and cough requiring palliation during the course of their illness**25,27,28,29.

**DYSPNOEA**

Shortness of breath, or dyspnoea, is a “term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, social, and environmental factors, and may induce secondary physiological and behavioural responses”33.

For patients it is impossible to separate the physical sensation from the emotional response34. Patients report feelings of anxiety, fear and panic, frequently accompanied by a sense of impending death. Breathlessness is frequently intermittent, usually being triggered by exertion or occasionally, emotion. Shortness of breath imposes numerous restrictions on activity, functioning inside and outside the home, and social life35. In one study of lung cancer patients, those with high dyspnoea scores had lower quality of life36.

The genesis and pathophysiology of dyspnoea is poorly understood, with multiple mechanisms possibly involved and patients using a range of descriptive terms. Intensity is possibly best measured using a visual analogue scale (VAS) while the Borg Category scale provides a range of descriptors and assesses the effect of exertion on the symptom37. Objective measures of respiratory function using spirometry were not shown to be a reliable guide to subjective levels of dyspnoea reported by cancer patients using a visual analogue scale38.
In advanced lung cancer, dyspnoea is usually multifactorial. Reversible physical causes should be treated, such as:

- optimising management of pre-existing COPD with bronchodilators and steroids
- managing pleural effusion: thoracentesis, pleurodesis (pleuroperitoneal shunt)
- management of bronchial obstruction with laser, radiotherapy, stent
- controlling cardiac failure
- using anticoagulation therapy for pulmonary embolism
- correcting anaemia
- treating infection
- controlling chest pain.

The overriding principle of palliation remains – is the treatment appropriate to the stage of the patient’s illness and in accordance with their wishes and goals?

Dyspnoea is usually associated with high levels of anxiety, and symptomatic treatments are aimed at reducing anxiety and the sensation of breathlessness. However, it may not be possible to relieve the symptom of dyspnoea completely.

Non-pharmacological interventions for breathlessness in lung cancer have been reported to be successful, with improvement in distress from breathlessness, and functional capacity following three to six weeks of an integrative model of care involving breathing retraining, relaxation and teaching coping and adaptive strategies. Other non-pharmacological measures for reduction of dyspnoea include the use of a bedside fan, particularly directing cool air onto the cheeks. Acupuncture was effective in an open pilot study.

**Pharmacological treatment of dyspnoea**

Most studies of the role of opioids to reduce dyspnoea have been carried out in healthy subjects or in patients with COPD where there is little evidence to support their use. A few small, largely uncontrolled studies have looked at the role of morphine to relieve dyspnoea in patients with advanced cancer. In this very ill population of patients, high dropout rates occur. Side effects included increased sedation.

Patients did report improvement in dyspnoea as rated on visual analogue scales. One randomised, placebo-controlled study of patients with dyspnoea and pain showed a reduction in dyspnoea with subcutaneous morphine. Morphine is recommended for symptomatic relief of dyspnoea on the basis of its action as a respiratory sedative and its possible role in resetting the sensitivity of the respiratory response to hypercapnea. Intermittent dosing is appropriate if dyspnoea is not continuous. The use of a concomitant antiemetic should be considered, and regular laxatives commenced.
Nebulized morphine has been shown to be of benefit in some case series of cancer patients, particularly in relation to the quality of the dyspnoea reported, but randomised controlled trials are lacking and benefit is largely unproven. In one study which did demonstrate benefit, the effect appeared to be more pronounced in patients who were already using oral opioids, occurred within the first 24 hours, and patients needed to be able to tolerate the mask or mouthpiece used in the nebulized route. There is no consensus on the optimal drug, dose, or schedule for administration, but it has been suggested that the dose needs to be in the order of 20mg morphine sulphate (intravenous solution). Bioavailability of nebulized morphine appears to be low, but it should not be assumed that it is safe to use oral and nebulized routes simultaneously. Nebulized morphine has resulted in bronchospasm, which has not been observed so far with nebulized fentanyl.

Nebulized lignocaine at two dose levels has also been tried in a small series for breathlessness, but was no more effective than nebulized saline.

Anxiolytics have also been used to relieve dyspnoea, and although results are not encouraging for long-term use, a trial of anxiolytic therapy on an individual basis is recommended. In unrelieved distress from severe dyspnoea, sedation using chlorpromazine, or a benzodiazepine such as diazepam or midazolam is recommended.

Steroids may have a role in reducing dyspnoea by decreasing airway inflammation and oedema, particularly in lymphangitis carcinomatosis, and may also be useful temporarily in major airway obstruction.

Palliative home oxygen therapy

Home oxygen therapy is normally reserved for patients with demonstrated chronic hypoxaemia caused by chronic airflow obstruction. In these patients continuous oxygen therapy (for more than 15 hours/day) may improve quality of life and decrease mortality.

For patients with dyspnoea associated with terminal lung cancer, the palliative effect of home oxygen may be over and above any effect on hypoxaemia. Supplemental oxygen has been shown to reduce dyspnoea in cancer patients who are hypoxic and symptomatic at rest. However, in another single-blinded cross over study of dyspnoeic cancer patients, half of whom had carcinoma of the lung and who had not previously used oxygen therapy, dyspnoea was relieved to the same extent by oxygen or medical air. The improvement in dyspnoea with oxygen could not be predicted by the level of hypoxia, and was potentiated by morphine and benzodiazepines but particularly benzodiazepines.
COUNSELING, BREATHING RETRAINING, RELAXATION,
and teaching coping and adaptive strategies
can improve dyspnoea and functional capacity
in lung cancer patients.

- Level of Evidence: II, IV
- Refs: 42, 64

OTHER NON-PHARMACOLOGICAL MEASURES TO BE
considered for dyspnoea include acupuncture
as a complementary procedure.

- Level of Evidence: IV
- Refs: 34, 45

A Therapeutic trial of morphine and/or
benzodiazepines is recommended for dyspnoea
in patients with advanced cancer:

- Level of Evidence: II, IV
- Refs: 49, 65

NEBULIZED MORPHINE CAN IMPROVE DYSPNOEA IN
some terminally ill lung cancer patients. A supervised
therapeutic trial may be worthwhile.

- Level of Evidence: III–3, IV
- Refs: 53, 57, 58

NEBULIZED LIGNOCaine HAS NOT PROVEN TO BE BETTER
than nebulized saline in relief of breathlessness.

- Level of Evidence: IV
- Refs: 61

COUGH

Cough has been reported as a symptom in 29–83% of palliative care patients. Persistent cough can be exhausting, can exacerbate chest wall pain, add to insomnia, and trigger vomiting at times. In patients with lung cancer, cough may be productive, with mucus, infected sputum, or blood expectorated, or non-productive, triggered by distortion of bronchial mucosa by endobronchial tumour. Other non-cancer causes of cough should be considered, such as cardiac failure, asthma or the use of angiotensin converting enzyme (ACE) inhibitors.

Simple measures such as change in posture at night may help. Cough suppression by various linctuses often with codeine, pholcodeine, or dextramethorphan is usually first line. Their action may depend more on the sugar content, as only limited pharmacological activity has been detected at the dose of opioid included. Morphine has been demonstrated to suppress cough and other opioids including methadone have been recommended, but there is little evidence to choose one opioid from another for its anti-tussive effect.
Nebulized lignocaine (5ml 1–2% up to four times daily) can be useful as a cough suppressant. The patient should fast immediately after use, but clear water is allowed and fasting only recommended for one hour in the palliative care setting. Nebulized bronchodilators should be available in case of bronchospasm. Inhaled sodium cromoglycate has been shown to reduce cough in NSCLC in one small randomised controlled trial. Expectorants and mucolytics appear to have little role. Nebulized saline can improve the effectiveness of coughing by loosening mucus.

The use of antibiotics to treat a chest infection in a dying patient will need careful discussion with patient and family but may be indicated to improve comfort. If secretions are troublesome and the patient is unable to expectorate, measures to reduce secretions should be tried, for example hyoscine hydrobromide, atropine or glycopyrrolate.

<table>
<thead>
<tr>
<th>Guidelines – Cough Suppression</th>
<th>Level of Evidence</th>
<th>Refs</th>
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<tbody>
<tr>
<td>Oral opioids are recommended for suppression of non-productive cough in lung cancer</td>
<td>II</td>
<td>66,67</td>
</tr>
<tr>
<td>Inhaled sodium cromoglycate could be tried in cough from non-small cell lung cancer that is resistant to standard therapy.</td>
<td>II</td>
<td>69</td>
</tr>
<tr>
<td>Nebulised lignocaine can be useful as a cough suppressant - special precautions need to be taken (see text).</td>
<td>IV</td>
<td>51</td>
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</table>

**HAEMOPTYSIS**

Haemoptysis can range from recurrent coughing of specks of blood, to massive, catastrophic haemorrhage (rare). It is important to exclude bleeding from other sites such as the nose or oropharynx. Radiotherapy or endobronchial laser may be used to control bleeding depending on the cause and prognosis. Oral fibrinolytic inhibitors, tranexamic acid and aminocaproic acid have been used in patients unable to undergo other treatments.

Massive haemoptysis is widely feared, but occurs rarely. Even so, preparation is useful. If there has been a warning of prior smaller bleeds, it may be important to discuss further resuscitative steps, but the level of detail in this discussion is a matter for judgment. Opioids and a benzodiazepine such as midazolam or diazepam should be readily available, and can be injected intravenously (if available), the rate titrated to the patient’s level of panic and consciousness.
MALIGNANT AIRWAY OBSTRUCTION

On occasions endobronchial lung malignancy may cause atelectasis, pneumonia or airway obstruction. Should the obstructive lesion be either inoperable or recurrent after previous resection the therapeutic options are limited. Chemotherapy is either ineffective or provides a brief response. Urgent radiotherapy can take several days to achieve an effect, so some mechanical or direct local approach may be necessary in the interval.

“The ability to manage acute airway obstruction can be life saving, airway relief should be expeditious and immediate, with low morbidity and mortality. It should not interfere with future definitive therapy. In patients with terminal malignancy, it should be economical in costs and should minimize hospitalisation.”

A number of techniques and appliances from coring out the tumour and application of cryotherapy to a range of stents, laser therapy and balloon dilatation are available. Reference to a succinct review of the subject is advised.

PAIN MANAGEMENT

Reported prevalence of pain in cancer patients in general ranges between 33–88% increasing to 60–88% in advanced cancer. The majority of cancer pain should be controllable. Unrelieved or poorly controlled pain leads to increased anxiety about the future and general anxiety that interferes with daily living. Early recognition and accurate diagnosis is important. There may be more than one type of pain present and a detailed history for each pain is important. Recognition of the type of pain involved will lead to more accurate prescribing of analgesics and co-analgesics. Neuropathic pain can be recognised by words such as burning, pins and needles, or pain in the distribution of a nerve or dermatome, or the presence of allodynia (pain provoked by light touch).

Table 1–7 Pain unrelated to the cancer or pain related to treatment

<table>
<thead>
<tr>
<th>Nociceptive pain syndromes:</th>
<th>Somatic: Bone metastases</th>
<th>Liver metastases-capsule distension</th>
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</thead>
<tbody>
<tr>
<td>Visceral: Nodal metastases</td>
<td>Mediastinal disease</td>
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<tr>
<th>Neuropathic pain syndromes associated with lung cancer:</th>
<th>Pancoast syndrome</th>
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<tbody>
<tr>
<td>(brachial plexus involvement from apical lung cancer)</td>
<td></td>
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<tr>
<td>Post-thoracotomy neuropathic chest wall pain</td>
<td></td>
</tr>
<tr>
<td>Neuropathic syndromes secondary to vertebral or para-vertebral metastases</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mixed neuropathic and nociceptive pain syndromes:</th>
<th>Tumour invasion of chest wall</th>
</tr>
</thead>
</table>

†For example, mucositis from chemotherapy, dysphagia secondary to radiotherapy
Pain assessment includes:

- a detailed history of each pain, full examination, and psychosocial assessment
- a history of analgesics already used and the response to them
- investigations to confirm the diagnosis, depending on the stage of the disease and the treatment options
- contributions from the multidisciplinary team.

Perception of pain in cancer will be influenced by the meaning of the pain for the patient. Worsening pain is often taken to mean disease progression, with the fear of escalating, uncontrolled pain and a painful death. Open discussion, allowing fears to be discussed, providing explanation of the symptom and reassurance of continued support is important.

Analgesics are the mainstay of treatment of cancer pain but awareness of other modalities is important including psychological supportive therapies, relaxation, emotional support, massage and acupuncture. Anti-cancer therapies may be important for pain relief, for example, radiotherapy for bone pain or neuropathic pain (due to tumour compression of nerves).

The treatment plan and follow-up program should be clearly communicated to all involved in caring; family, general practitioner and community services.

**Morphine for cancer pain**

Pain relief usually commences with regular mild analgesics for example, regular paracetamol, with appropriate co-analgesics (see below). Although the World Health Organization (WHO) method for control of cancer pain describes progression to a weak opioid, for example codeine with paracetamol\(^7^5\), current palliative care practice does not recommend this step. The presence of paracetamol limits dose escalation leading to inadequate pain relief, and regular codeine can lead to severe constipation.

Morphine is the drug of choice for moderate to severe cancer pain. Persistent pain calls for regular analgesia, with the aim of achieving pain relief at night and by day, and both at rest and on movement. Morphine has been safely used for cancer pain without development of tolerance or addiction, the most significant side effects being constipation, nausea and vomiting\(^7^6\). However, many patients with lung cancer also have COPD, and the use of opioids has at times been limited by the fear of respiratory depression. Unlike normal experimental subjects and post-operative patients, opioid-induced respiratory depression did not occur in a group of cancer patients who were fully pain-controlled on a stable dose of oral morphine. A majority of this group had pre-existing COPD and/or carcinoma of the bronchus\(^7^7\).
The principles of pain relief using morphine (or any other opioid) include:

- **Dose titration** using a short acting formulation, for example, morphine mixture four hourly until stable 24 hour dose requirements are established.
- **Introduction of a slow release formulation** to provide continuous background analgesia.
- **Provision of an immediate release formulation** for breakthrough pain or for incident pain.
- **Choice of the simplest available route** for example oral, then subcutaneous or rectal.
- **Anticipation of any side effects** for example, prescribing an antiemetic for nausea (patients need to be warned of early side effects of possible nausea and some drowsiness initially), and introduction of regular laxatives to prevent constipation.
- **If frequent breakthrough doses are required**, the background dose should be increased in line with breakthrough requirements. In opioid prescribing there is no ceiling dose; the dose can be increased in response to unrelieved pain unless side effects supervene.

Despite the emphasis on the oral route for drug delivery in palliative care, in the case of severe, uncontrolled pain, the intravenous route may be the most appropriate way to achieve rapid pain control.

Many patients harbour concerns about addiction when using morphine, but their fears are unfounded. If pain is reduced by another modality, for example, radiotherapy to painful bone metastases or an apical lung cancer, then morphine can be reduced. This is usually done gradually, but if the dose reduction is not sufficient the side effects of nausea and drowsiness will reappear.

If there are persistent side effects such as nausea, drowsiness or confusion, in the face of inadequate pain control, then the situation must be reassessed. If the pain is opioid responsive, it may be possible to change to another opioid and escalate the dose successfully, for example fentanyl, hydromorphone or methadone. Methadone is re-emerging as having a useful role in poorly responsive pain, possibly due to N-methyl-D-aspartate (NMDA) activity. Previous equianalgesic opioid dose tables should be ignored, as methadone dose equivalence varies with prior opioid dose.

If the pain is poorly opioid-responsive, for example neuropathic pain, or bone pain, then co-analgesics should be introduced.

Care should always be taken with opioid doses in the elderly and in the use of morphine in patients with renal failure.
Unrelieved or poorly controlled pain leads to increased anxiety about the future and general anxiety that interferes with daily living.

Management of moderate to severe cancer pain should include the appropriate introduction and dose titration of opioids.

**Anti-inflammatories and co-analgesics in cancer pain**

Non-steroidal anti-inflammatory drugs or the new cyclooxygenase (COX) II inhibitors appear to have an important role in cancer pain, particularly when there is bone pain or pain due to chest wall infiltration. The usual precautions and dose ceilings apply.

A range of drugs has been used in neuropathic pain syndromes in other settings:
- tricyclic antidepressants
- membrane stabilising drugs including anti-convulsants
- local anaesthetics systemically or oral derivatives, for example, mexiletine, flecainide
- NMDA receptor antagonists, for example, ketamine
- steroids for nerve compression.

**Guideline – Neuropathic Pain Management**

Extrapolation from therapeutic approaches to neuropathic pain in other diseases indicates that antidepressants and anti-convulsants offer effective palliation.

**Referral to a specialist pain clinic for consideration of a nerve block or spinal analgesia is recommended if pain is not well controlled.**

**CONSTIPATION**

Constipation is a frequent and troublesome symptom in advanced cancer due to reduced mobility, reduced fibre and fluid intake and the use of opioids. In a lung cancer patient with dyspnoea, constipation can be a cause of severe distress. In one study of hospice inpatients, laxatives were required by 64% of those not using opioids and 87% of those using strong oral opioids. The use of fentanyl for analgesia is associated with less need for laxatives.
for laxatives than the use of morphine\textsuperscript{80}. The best laxative for terminally ill patients using opioids is yet to be determined, but in one study senna and lactulose showed equal efficacy, with senna being recommended on the basis of cost\textsuperscript{81}.

<table>
<thead>
<tr>
<th>Guideline – Bowel Care</th>
<th>Level of Evidence</th>
<th>Refs</th>
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<tbody>
<tr>
<td>The best laxative for terminally ill patients using opioids is yet to be determined. Senna and lactulose have shown equal efficacy.</td>
<td>III–3</td>
<td>81</td>
</tr>
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</table>

**OUTCOMES IN PALLIATIVE CARE**

Studies already undertaken highlight the difficulty of capturing the complexity of the outcomes in palliative care for both the patients and their relatives\textsuperscript{19,82}. A number of outcome measures have been used in clinical audit in palliative care, but as yet there is no ‘ideal tool’\textsuperscript{9}. As symptoms worsen with increasing disease and approaching death, symptom assessment scales appear to reflect overall deterioration, rather than poor symptom control\textsuperscript{83}.

Satisfaction with care has been suggested as a suitable outcome to assess quality of care\textsuperscript{84}. However, it has been argued that patient satisfaction ratings are uniformly high whatever model of care is examined and do not give useful information leading to change\textsuperscript{89}. One promising tool developed to measure family satisfaction with care in advanced cancer is the FAMCARE Scale\textsuperscript{85}.

Cost-effectiveness of palliative care is rarely assessed. Increasing resources to better co-ordinate services for patients at home, to avoid the possibility of inefficient duplication of services to some patients and lack of services to others, resulted in a decrease in the overall cost of the services provided, particularly through avoiding inpatient admissions and utilisation of nurse home visits. There was no discernible difference to patient and family outcomes\textsuperscript{86}.

A national study in the UK, where hospice and palliative care services are well established, demonstrated that there is still inadequate symptom control, particularly relating to pain and dyspnoea, as well as inadequate home services and difficulty in obtaining information\textsuperscript{23}. The need for education in palliative care and further resources was highlighted.

(With acknowledgement to *Clinical practice guidelines for the management of advanced breast cancer.*)
7.2 SPECIAL PROBLEMS IN SUPPORTIVE CARE AND CARE OF ADVANCED LUNG CANCER

PLEURAL EFFUSION

The presence of an ipsilateral pleural effusion in association with a newly diagnosed NSCLC is a poor prognostic sign. Thoracocentesis should be performed with all the aspirated fluid sent for cytological evaluation including cell block preparation. If the cytology result is positive for malignant cells the prognosis is extremely poor and palliative management is appropriate including control of the malignant effusion if it recurs and causes symptoms. In the past this has often been done by intercostal tube drainage, with the tube left in place until the drainage falls to less than 100ml per day, and chemical pleurodesis by doxycycline or bleomycin. With the advent of thoracoscopic techniques the preferred approach now for recurrent symptomatic pleural effusion is thoracoscopic assessment under general anaesthetic, drainage of all the fluid and talc insufflation. This provides effective palliation provided the lung is capable of re-expansion. In a recent Australian review of this approach in 61 patients, 18 with lung cancer, the overall median survival was 220 days (115 days for lung cancer) and the 30 day mortality was zero. The ability to completely drain all fluid and obtain full lung expansion would appear to be a contributing factor.

In patients with poor prognosis, or those in whom it is anticipated that chemotherapy will control the effusion, simple pleural aspiration may be sufficient to relieve symptoms. A retrospective audit of technique has been described which has identified a reduced rate of post-aspiration pneumothorax (p=0.0189) using an eight French gauge trocar and cannula, three way tap and sealed bag system.

<table>
<thead>
<tr>
<th>Guideline – Management of Pleural Effusion</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion is best managed by talc insufflation following thoracoscopic exploration and complete drainage of fluid.</td>
<td>IV</td>
<td>87</td>
</tr>
</tbody>
</table>

PERICARDIAL EFFUSION

Symptomatic malignant pericardial effusions occur uncommonly in NSCLC and are a poor prognostic sign. Confirmation of the clinical diagnosis is by echocardiograph. If the effusion is of a significant size and causing right ventricular compression, it is best treated by pericardiocentesis under echocardiographic control by an experienced cardiologist. A pigtail catheter is inserted and left in place until there is minimal drainage and a sclerosing agent such as bleomycin can be instilled through the catheter prior to its removal.

152 Clinical practice guidelines for the prevention, diagnosis and management of lung cancer
In NSCLC it is rarely indicated to proceed to a pericardial window for a malignant pericardial effusion secondary to the lung cancer.

<table>
<thead>
<tr>
<th>Guideline – Management of Pericardial Effusion</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardiocentesis can be safely performed under echocardiographic control. The outcome is effective.</td>
<td>IV</td>
<td>89</td>
</tr>
</tbody>
</table>

**UNILATERAL VOCAL CORD PARALYSIS**

Unilateral vocal cord paralysis is observed with both NSCLC and SCLC with significant mediastinal lymph node involvement on the left side. In this situation, treatment of the unilateral vocal cord paresis is palliation of significant symptoms, most commonly significant hoarseness, loss of volume, decreased phonation time and decreased vocal range as well as a significant incidence of aspiration.

In NSCLC there is also an incidence of unilateral vocal cord paresis following radical surgery for centrally placed left sided lung cancers when the left recurrent laryngeal nerve may be damaged or deliberately divided in an attempt to provide curative surgical results. In these cases, depending on the stage of the disease, there may be prolonged survival with the symptoms related to the vocal paresis, as opposed to the former group, where the prognosis is poor and most patients do not survive 12 months.

There are two principal procedures available; either injection laryngoplasty with teflon or thyroplasty, in which a window is created in the thyroid cartilage at the level of the vocal cords and a pre-fabricated dense hydroxyapatite implant is placed to bring the paralysed vocal cord to the midline. In the past, teflon injections were used more often but thyroplasty is becoming the procedure of choice because of a trend to superior voice and swallow outcomes. Following teflon laryngoplasty satisfactory phonation is achieved in over 85% of patients whilst the success rate with thyroplasty is slightly better, although the choice of procedure has not been subject to randomised study. Both procedures improve vocal and aspiration symptoms.

**HYPERCALCAEMIA: SEVERE HYPERCALCAEMIA IS A MEDICAL EMERGENCY**

(with acknowledgement to Clinical practice guidelines for the management of advanced breast cancer)

Hypercalcaemia is a well recognised complication in lung cancer, occurring as a paraneoplastic phenomenon as well as in the presence of bone metastases. Among its many symptoms are thirst, polyuria, polydipsia, nausea and vomiting, constipation, muscle weakness, worsening of pain, confusion and obtundation. Mild cases may be difficult to recognise. In severe cases it can lead to death through renal failure, cardiac arrest or coma.
Treatment of severe hypercalcaemia involves rehydration (with up to six litres per day of normal saline) plus a drug to stabilise calcium levels. Currently the best drugs belong to the bisphosphonate group, which includes pamidronate and sodium clodronate (see chapter 8, p169). Pamidronate is given intravenously over two to four hours in a dose of 30–90mg, depending on the level of serum calcium. It leads to lowering of serum calcium within 24 to 96 hours. It may be more effective than intravenous sodium clodronate in severe cases.

References


8. PALLIATIVE RADIATION

8.1 Thoracic symptoms

8.2 Superior vena cava obstruction

8.3 Spinal cord compression

8.4 Bone metastases
   Solitary lesions
   Pathological fractures
   Treatment of bone metastases
      Radiotherapy
      Chemotherapy
      Bisphosphonates
      Orthopaedic management
   Mechanisms of fracture and risk assessment
      General principles for prophylactic fixation

8.5 Brain metastases
8.1 THORACIC SYMPTOMS

The Medical Research Council in the UK has published on a series of studies investigating the role of radiotherapy in the symptomatic management of locally advanced intrathoracic disease\(^1\). Radiotherapy improved symptoms of haemoptysis, chest pain, dyspnoea and cough in 49–97% of patients studied. In the patient groups studied, there was no advantage with respect to palliation of symptoms in giving longer courses of radiotherapy, with poor prognosis patients gaining the same benefit from one fraction of radiotherapy compared to two, and in a slightly better prognosis group, two fractions of radiotherapy gave the same benefit as 10 fractions\(^{1,2,3}\). A third study, in the series of studies in patients with good performance status, compared two fractions of treatment with a 13-fraction course. The two fraction group achieved more rapid palliation and had less dysphagia, but survival was longer in patients randomised to the higher dose\(^4\).

Similarly, a National Cancer Institute of Canada randomised study also showed improved survival in patients receiving 20Gy in five fractions when compared to patients receiving a single 10Gy fraction of treatment. This study again showed no difference in palliation of symptoms between the two trial arms\(^5\).

An Australian randomised study showed no benefit in adding 5-fluorouracil to a palliative course of radiotherapy, with an improved response rate in the combined treatment arm not being translated into better symptom control, but resulting in increased toxicity\(^6\). A randomised study comparing endobronchial brachytherapy and external beam radiotherapy for palliation of symptoms from inoperable NSCLC showed external beam treatment provided better overall and more sustained palliation with fewer retreatments\(^7\). A second randomised study which included patients with early stage disease, as well as more advanced cases (the rationale for treatment of these different groups is unclear) has shown that the addition of brachytherapy to external beam radiotherapy can provide short term improvement in dyspnoea scores, particularly in patients with obstructing tumours in the main bronchi causing atelectasis\(^8\).
Radiotherapy is an effective modality for the management of certain symptoms caused by uncontrolled intrathoracic disease, and short courses of radiotherapy are as effective as more fractionated regimens.

There appears to be improved survival in patients with a good performance status receiving higher doses of palliative radiotherapy, compared to single or two fraction courses.

External beam radiotherapy appears to provide better palliation compared to endobronchial brachytherapy, but brachytherapy might be of benefit in patients with endobronchial obstructing lesions.

### 8.2 SUPERIOR VENA CAVA OBSTRUCTION

Lung cancer accounts for approximately 80% of cases of superior vena cava obstruction (SVCO). Treatment without an effort to obtain a histological diagnosis cannot be justified (the complication rate of mediastinoscopy—almost 100% successful in achieving a histological diagnosis—is less than 5%)\(^9\). The Cochrane Collaboration have conducted a systematic review of the subject and looked at 90 studies in which 2816 patients with either SCLC or NSCLC were accrued. The rates of relief of symptoms in SVCO in SCLC patients were 83% (216/260) and 76% (137/180) using chemotherapy and radiotherapy respectively, whilst synchronous chemo-radiotherapy provided relief of 87% patients (33/38). In NSCLC, radiotherapy relieved SVCO in 64% patients (105/165). Stent insertion relieved SVCO in 94% (135/143) of both SCLC and NSCLC patients\(^10\). In a prospective randomised study looking at chemotherapy with or without radiotherapy in SCLC, 37 patients presented with SVCO. Nine of these relapsed or progressed during initial chemotherapy, but of the remaining 28 patients, 13 received chemotherapy alone and 15 chemotherapy and radiotherapy. This was, in effect, a subset analysis, and it did not show any benefit in adding radiotherapy after 12 weeks of cyclical chemotherapy\(^11\).
<table>
<thead>
<tr>
<th>Guidelines – Superior Vena Cava Obstruction in Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A histological diagnosis is desirable before treatment of superior vena cava obstruction.</td>
<td>IV</td>
<td>9</td>
</tr>
<tr>
<td>Chemotherapy on its own is effective in superior vena cava obstruction due to small cell lung cancer.</td>
<td>II</td>
<td>10,11</td>
</tr>
</tbody>
</table>

### 8.3 SPINAL CORD COMPRESSION

Spinal cord compression is a medical emergency and urgent multidisciplinary management is advisable, with early diagnosis a powerful predictor of outcome\(^\text{12}\).

Patients who are known to have bony metastatic disease, and their carers, should be warned about the possibility and educated regarding the early symptoms of spinal cord compression, and encouraged to notify such symptoms as soon as possible. Primary medical carers should also be aware of the risks of spinal cord compression and paraplegia and the importance of prompt action. Symptoms suggestive of spinal cord compression should be investigated in the absence of signs.

If spinal cord compression is suspected, whether on symptomatic or clinical grounds, the investigation of choice is MRI scan\(^\text{13}\). MRI is non-invasive and the precise level or levels of cord compression can be ascertained. If MRI is not available, then plain x-rays and CT myelogram should be used\(^\text{14}\).

Dexamethasone should be started on suspicion of spinal cord compression and whilst awaiting assessment\(^\text{15}\). A randomised study has shown that the addition of high-dose dexamethasone to radiotherapy for spinal cord compression improves gait function after treatment\(^\text{16}\).

Patients presenting with suspected spinal cord compression should be reviewed as early as possible by a radiation oncologist and considered for review by an orthopaedic surgeon or neurosurgeon with an interest and expertise in spinal problems. A recently reported randomised trial compared decompressive surgical resection followed by radiotherapy with radiotherapy alone in patients with spinal cord compression caused by metastasis from a variety of tumour sites, of which lung was the most common\(^\text{17}\). Patients randomised to surgery retained the ability to walk significantly longer than those treated with radiotherapy alone, although survival was not significantly different between the arms. Based on this study, surgery followed by radiotherapy should be considered the treatment of choice in most patients.
Surgical intervention should also be considered in the following situations:
• solitary vertebral compression in a patient without previous diagnosis of malignancy
• pathological fracture or dislocation causing compression
• progressive disease while on radiotherapy or in previously irradiated site.

When surgery is not considered appropriate, radiotherapy should be started immediately. Patients who are ambulatory and retain bladder or bowel function prior to the commencement of radiotherapy have the most favourable neurological outcome\textsuperscript{12,18,19}.

**KEY POINTS:**
• Spinal cord compression is a medical emergency and urgent multidisciplinary management is advisable.
• Patients who are ambulatory and retain bladder or bowel function prior to the commencement of radiotherapy have the most favourable neurological outcome\textsuperscript{12,18,19}.

<table>
<thead>
<tr>
<th>Guidelines – Management of Metastatic Spinal Cord Compression</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone should be started on suspicion of spinal cord compression and whilst awaiting assessment.</td>
<td>II [III–3]</td>
<td>15, 16</td>
</tr>
<tr>
<td>If spinal cord compression is suspected, whether on symptomatic or clinical grounds the investigation of choice is MRI scan.</td>
<td>III–3</td>
<td>13, 14</td>
</tr>
<tr>
<td>Surgery followed by radiotherapy is the treatment of choice for spinal cord compression.</td>
<td>II</td>
<td>17</td>
</tr>
<tr>
<td>When surgery is not considered appropriate, radiotherapy should be started immediately. Radiotherapy is considered as effective as surgery in achieving symptomatic relief.</td>
<td>III–3</td>
<td>12, 18, 19</td>
</tr>
</tbody>
</table>
8.4 BONE METASTASES

A significant proportion of patients with metastatic lung cancer will have bony metastases. Most will be painful and some lead to pathological fracture (approximately 9%)\textsuperscript{20}.

Symptoms suggestive of bone metastasis such as persistent, severe or unexplained bone pain, particularly worse at night and interfering with sleep, warrant investigation, initially with a plain x-ray. A radioisotope bone scan may help determine the extent and number of metastases. CT or MRI scans may be useful if doubt remains about the diagnosis.

SOLITARY LESIONS

It is important to ensure that a solitary lesion is a metastasis before treatment. In such cases the clinical situation of the patient (for example, a long disease-free interval after initial treatment for lung cancer) is important and the use of bone biopsy should not be excluded. If x-ray and bone scan suggest a solitary metastasis in the vertebrae, MRI should be performed. This may reveal that the lesion is not solitary or that it has characteristics of a metastasis.

PATHOLOGICAL FRACTURES

A pathological fracture may be the first presentation of a bony metastasis. It is most common in the proximal femur.

Orthopaedic referral is required if:
- 50% of bone cortex is lost in a long bone;
- pain is present with over 50% of vertebral body destruction and/or pedicle destruction without collapse;
- moderate deformity and collapse is present\textsuperscript{21}.

TREATMENT OF BONY METASTASES

The treatment of bony metastases has two aims: to reduce pain and to reduce the risk of fracture particularly in long bones. The available treatments include radiotherapy, chemotherapy, bisphosphonates and internal fixation/replacement (as discussed below).
RADIOTHERAPY

Palliative radiotherapy is a very important modality in the management of metastatic bone pain. Over 40% of patients can expect at least 50% pain relief at one month, and just under 30% can expect complete pain relief at one month²⁰. Various schedules of treatment are used and randomised studies have not shown a marked difference in pain relief from any particular schedule²².

The pathophysiology of bone pain from metastases and the mechanism of pain relief from radiotherapy are unclear²³. Recent trials have shown that 8Gy single fraction is as efficacious for pain relief as other schedules²²,²⁴,²⁵,²⁶,²⁷,²⁸. Further trials may define those patients who would benefit from fractionated radiotherapy²². The optimum schedule following elective pinning of lytic lesions has not been determined.

Lesions in long bones should be assessed in conjunction with an orthopaedic surgeon and if the risk of fracture is considered high enough, then elective internal fixation is indicated. This should always be followed by radiation treatment²⁹. The aim of the radiation is not only to relieve the pain but also to cause tumour regression and subsequent healing.

In patients who have widespread bony lesions consideration can be given to single fraction hemi-body radiation treatment. Doses of 8Gy to the lower hemi-body and 6Gy to the upper hemi-body are well tolerated with modern anti-emetics, and are able to give considerable relief with little morbidity provided blood counts are satisfactory³⁰,³¹.

Systemic radiation therapy with bone-seeking radioisotopes may be helpful when there is a preponderance of sclerotic lesions, although the evidence on which this is based relates predominantly to patients with breast and prostate cancer³².

<table>
<thead>
<tr>
<th>Guidelines – Radiotherapy in Management of Skeletal Metastases</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palliative radiotherapy remains the most effective single modality for the treatment of local metastatic bone pain.</td>
<td>IV</td>
<td>20</td>
</tr>
<tr>
<td>In the treatment of skeletal metastases trials have shown that 8Gy single fraction is as efficacious for pain relief as other schedules.</td>
<td>II</td>
<td>22,24,25, 26,27,28</td>
</tr>
<tr>
<td>In patients who have widespread bony lesions consideration can be given to single fraction hemi-body radiation palliation.</td>
<td>III–2</td>
<td>31</td>
</tr>
</tbody>
</table>
CHEMOTHERAPY

Chemotherapy is worth considering in people with bone metastases, particularly those multifocal, symptomatic disease not controlled by simpler measures. This includes people with many symptomatic bone metastases, and people with coexisting visceral metastases that need immediate treatment (see chapter 5.5, p97).

BISPHOSPHONATES

Bisphosphonates like clodronate, palmidronate and zoledronate inhibit osteoclastic bone resorption and have an established role in the treatment of hypercalcaemia associated with malignancy. Bisphosphonates improve pain in people with symptomatic bone metastases from solid tumours including lung cancer. Bisphosphonates also reduce the incidence of skeletal events in people with multiple myeloma or bone metastases from breast cancer. A study recently reported in abstract form suggests that bisphosphonates may also reduce the rate of skeletal events in people with a range of solid tumours, including NSCLC.

Bisphosphonates are generally well tolerated and the risk of serious side effects is low. The most common side effects of parenteral bisphosphonates are fever, flare of bone pain and myalgia in the 24 hours after infusion. Oral bisphosphonates may cause oesophageal discomfort and irritation.

<table>
<thead>
<tr>
<th>Guideline – Bisphosphonates in Management of Bone Metastases</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates improve pain in people with symptomatic bone metastases from lung cancer.</td>
<td>1</td>
<td>33,34,35</td>
</tr>
</tbody>
</table>

ORTHOPAEDIC MANAGEMENT

Whilst radiotherapy can relieve bone pain when no significant mechanical failure has occurred, it is quite ineffective in circumstances in which a fracture in a weight-bearing bone has occurred or is inevitable.

Orthopaedic management falls into three categories:

- prophylactic fixation of long bone deposits, where there is a risk of fracture
- stabilisation or reconstruction following pathological fracture
- decompression of the spinal cord and nerve roots, followed by stabilisation of the affected vertebra.
MECHANISMS OF FRACTURE AND RISK ASSESSMENT

As a general rule, when 50% of a cortex in a long bone has been destroyed fracture is likely. Prophylactic fixation should be performed prior to radiotherapy. Avulsion of the lesser tuberosity is an indication of imminent hip fracture. Any erosion of the femoral neck is an indication for prophylactic fixation.

GENERAL PRINCIPLES FOR PROPHYLACTIC FIXATION ARE THAT:

- the procedure should provide immediate stability
- the surgeon must assume that the fracture will not unite
- the fixation should aim to last the lifetime of the patient

Whatever implant is used should restore sufficient strength to allow immediate unsupported use. In the lower limb, this includes weight bearing. If the implant alone cannot satisfy these criteria, it might need supplementation by other material such as cement, bone substitutes or endoprostheses.

Intramedullary nailing is indicated in fractures of the shaft of the femur, tibia or humerus. Osteosynthesis with a plate has only limited indications and should never be used in the lower limb. Cement, ceramic rings or one of the newer bone substitutes should be added to achieve immediate axial stability.

Intramedullary nailing of femoral lesions is associated with a significant risk of intraoperative embolism and death. Unpublished data suggest a significant risk of acute oxygen desaturation during surgery. Such procedures need adequate monitoring and preventative measures.

Non-weight bearing bones, such as ribs, fibula and much of the pelvis, can be safely treated with radiotherapy alone in most cases.

The whole of the bone that has a metastasis should be imaged to ensure that the most appropriate fixation is used. Patients with multiple deposits should have all lesions at risk treated, if possible. This aids nursing care and the provision of radiotherapy. If the patient is in the terminal phase of their illness, the limb should be splinted and the limb made comfortable.
8.5 BRAIN METASTASES

Cerebral metastases are common in lung cancer. The most common symptoms are focal neurological signs, headache, confusion, personality changes, nausea and vomiting.

Diagnosis is made by history, physical examination and CT and/or MRI scan. There is a lot of non-randomised evidence that prognostic factors are of overwhelming importance in determining outcome in patients with intracranial metastatic disease and careful assessment of patients is therefore vital. It is important to distinguish true cerebral metastatic disease from meningeal disease or bony disease of the skull impinging on the brain or base of the skull causing cranial nerve damage, as treatment will differ.

There is evidence that resection of a solitary intracranial metastasis followed by radiotherapy potentially results in increased local control and a longer disease-free survival than radiotherapy alone. It follows that patients presenting with an apparent solitary intracranial metastatic lesion should be staged to exclude extracranial metastatic disease, and the solitary nature of the brain metastasis confirmed with an MRI scan, if only a CT scan was performed to make the diagnosis. Stereotactic radiosurgery may be an alternative to surgical resection of a solitary brain metastasis and has been shown to be of benefit in patients with two to four intracranial metastases, in addition to whole-brain radiotherapy.

Metastases involving the cerebellum may require early intervention owing to their tendency to cause obstructive hydrocephalus and raise intracranial pressure. For this reason, these lesions are best managed with neurosurgical resection in patients who are fit enough. Radiotherapy on its own is not recommended.

Cerebral metastatic disease is rarely a medical emergency but does require early diagnosis and evaluation. Radiotherapy to the whole brain has been an accepted standard of care for patients with brain metastases. At least four randomised trials carried out by the Radiotherapy Oncology Group (RTOG) in America, the Royal College of Radiologists in Britain and a French group compared different whole brain radiotherapy doses ranging from 10Gy in a single fraction to 40Gy in 20 fractions, and showed no differences in symptom response rates or times to disease progression according to dose/fractionation schedule. The overall response rate of symptoms of cerebral metastases to radiotherapy is around 75–100%, depending upon symptom type. The main side effect of radiotherapy to the whole brain is inevitable complete alopecia. Hair will usually regrow after a two to three month period although it may be less dense than previously. Other acute side effects include lethargy, nausea, vomiting, headaches and ataxia, which altogether occur in around 10% of patients.

Dexamethasone is particularly useful in reducing cerebral oedema.

Re-irradiation for progressive brain metastases may be considered in selected patients without progressive disease at other sites.

Key point:

- The overall response rate of symptoms of cerebral metastases to radiotherapy is around 75–100%, depending upon symptom type.
### Guidelines – Irradiation and Radiotherapy for Skeletal Metastases

<table>
<thead>
<tr>
<th>Treatment Description</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy is effective palliation for brain metastases from lung cancer.</td>
<td>II</td>
<td>39,46,47,48</td>
</tr>
<tr>
<td>Resection of solitary cerebral metastases followed by radiotherapy potentially results in increased local control and a longer disease-free survival than radiotherapy alone.</td>
<td>III–2</td>
<td>40,42</td>
</tr>
<tr>
<td></td>
<td>III–3</td>
<td>43</td>
</tr>
<tr>
<td>Stereotactic radiosurgery may be a suitable alternative to resection.</td>
<td>III–3</td>
<td>43, 44</td>
</tr>
<tr>
<td>Doses of whole brain radiotherapy ranging from 10Gy in a single fraction to 40Gy in 20 fractions have similar effectiveness in symptom palliation and times to disease progression. Shorter courses, for example 20Gy in five fractions, are recommended because of patient convenience.</td>
<td>II</td>
<td>39,48,49,50</td>
</tr>
<tr>
<td>Re-irradiation for progressive brain metastases may be considered in selected patients without progressive disease at other sites.</td>
<td>IV</td>
<td>52</td>
</tr>
</tbody>
</table>

(This section on spinal cord compression, bony and brain metastases has been adapted with the permission of the National Breast Cancer Centre, from ‘Management of Advanced Breast Cancer – Clinical Practice Guidelines’. NHMRC-NBCC Canberra, January 2001, pp 90–1.)

### References

1. A Medical Research Council (MRC) Randomised Trial of Palliative Radiotherapy With Two Fractions or a Single Fraction in Patients With Inoperable Non-Small Cell Lung Cancer (NSCLC) and Poor Performance Status. Br J Cancer 1992; 65: 934–41.


9. ALTERNATIVE AND COMPLEMENTARY THERAPIES

9.1 General

9.2 Effectiveness, safety and cost
   - Effectiveness
   - Safety
   - Cost

9.3 Discussing alternative therapies
9.1 GENERAL

The term ‘alternative therapies’ is “used loosely to describe anything outside the orthodox circle of surgery, radiation and chemotherapy”¹. It includes different approaches that operate on the “hope that we can boost the immune system through a mind-body connection… these range from visualisation to diet and prayer…”².

Most alternative therapies have not been tested in randomised clinical trials. Alternative therapies may involve some interference with conventional therapies and may cause harm. Some alternative therapies have been acknowledged by the medical profession as useful, and these are usually known as complementary therapies. The effect of other alternative therapies is unknown or may cause harm. Complementary therapies can work alongside conventional therapies, whereas alternative therapies may involve some tension or interference with conventional therapies.

Educational and psychosocial care has been found to benefit adults with cancer in relation to alleviating anxiety, depression, mood, nausea, vomiting, pain and increasing knowledge.³ Both relaxation and meditation are frequently and effectively used by general practitioners and palliative care teams.

<table>
<thead>
<tr>
<th>Guideline – Educational and Psychosocial Care in Cancer</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational and psychosocial care has been found to benefit adults with cancer in relation to anxiety, depression, mood, nausea, vomiting, pain and knowledge.</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Alternative therapies, as they are referred to for the rest of this chapter, are used by many Australians. In a random sample of 3 004 South Australians, 48.5% of respondents (reflecting the general population) had used at least one non-physician-prescribed alternative medicine during the past year, while 20.3% had visited at least one alternative practitioner⁴.

Looking specifically at people with cancer, Begbie et al found that 21.9% of people attending one of three NSW oncology clinics said they were using alternative therapies⁵. Other studies, some overseas and some Australian, have found that 9–54% of adults with cancer⁶,⁷,⁸,⁹,¹⁰ and 46% of children with cancer¹¹ use alternative therapies.

Australians spent an estimated $309 million per year on alternative therapists and $621 million per year on alternative therapies in 1993, which far exceeds the patient contribution of $360 million to standard pharmaceuticals for 1992/93³.
The main reasons for using alternative therapies given in the Begbie et al study were:

- new source of hope (49% of users of alternative therapies)
- preference for natural therapy (40%)
- impression that it is a non-toxic therapy (37%)
- supportive alternative practitioner (29%)
- try something different (23%)
- greater personal involvement (14%).

The main therapies used were:

- relaxation/meditation (59% of users of alternative therapies)
- diet therapy (57%)
- megavitamins (43%)
- positive imagery (44%)
- faith/spiritual healing (30%)
- naturopathy (27%)
- immune therapy (17%)
- homeopathy (16%)
- acupuncture (11%).

Seventy-five percent of people using alternative therapies used more than one (median 3, range 1–8).

Even though there is no data examining specifically the use of alternative therapies in those with advanced lung cancer, there is no obvious reason why usage would not be similar to that of other people with cancer.

There are three important issues to consider in the use of alternative therapies, as there are with mainstream therapies: effectiveness, safety and cost.

### 9.2 EFFECTIVENESS, SAFETY AND COST

**EFFECTIVENESS**

There is little evidence that alternative therapies are effective. Most have not been examined rigorously, and some of those that have been examined have not been found to be effective.

In the USA, the National Institutes of Health have set up an Office of Alternative Medicine that aims to explore the merits of alternative therapies. Alternative therapies that concentrate on strengthening the mind-body relationship have been tested, and have been shown to be effective. For example, prayer is being tested in controlled...
clinical trials and thus far has been shown to be effective\textsuperscript{15}. Laughter has also been effective for some individuals\textsuperscript{16}. Relaxation and meditation have been tested and shown to be valuable\textsuperscript{17}.

Inhalation aromatherapy has been used in a placebo controlled blind randomised trial during radiotherapy in Australia.

The aromatic oils were administered by inhalation during radiotherapy with the aim of reducing anxiety level. Patients underwent anxiety assessments before and following completion of treatment. There was no difference in test scores in the randomly assigned groups. The anxiety scores were significantly lower (p=0.04) at treatment completion in those having carrier oil only as against those treated in the fragrant arms of the trial\textsuperscript{18}.

<table>
<thead>
<tr>
<th>Guideline – Aromatherapy and Anxiety in Radiotherapy</th>
<th>Level of Evidence</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatherapy has not been shown to reduce anxiety in patients with cancer undergoing radiotherapy.</td>
<td>II</td>
<td>18</td>
</tr>
</tbody>
</table>

In a recent initiative, the Federal Government has established a new unit to consider and evaluate complementary treatments\textsuperscript{19}.

**SAFETY**

Many alternative therapies requiring changes in diet should be safe, although when there is a danger of substantial weight loss, such diets should be avoided\textsuperscript{6}. Meditation and spiritual approaches appear to do no harm.

However, most alternative therapies involving the consumption of substances have not been assessed for safety. Their content is uncontrolled and may be quite variable\textsuperscript{20}. They may be adulterated with corticosteroids or other active compounds\textsuperscript{21}. They may be intrinsically toxic\textsuperscript{22}. There have been reports of deaths from royal jelly\textsuperscript{23}, and hepatitis from chaparral tea\textsuperscript{24}, which is a herbal remedy for cancer used by Native Americans.

There are concerns about the safety of megavitamins, particularly the fat-soluble vitamins\textsuperscript{25,26}. There is potential for high doses of vitamin A to cause headaches due to raised intracranial pressure\textsuperscript{27}. The safety of many other compounds, and their potential for cross-reactivity with standard therapies, is unknown. One problem that is known is the potential for those taking large doses of vitamin D or its derivatives to develop hypercalcaemia\textsuperscript{28}. 
There are also concerns about the knowledge base of alternative therapists. Some are well trained in their craft, but others are not. Most alternative therapists are not yet under state regulatory control. Potentially dangerous alternative therapies in those with advanced lung cancer include:

- taking calcium with or without vitamin D for bone disease, as this may exacerbate hypercalcaemia
- some diets recommended for treatment of cancer, such as the beetroot diet, the grape diet and the Gerson diet, as they may be nutritionally inadequate

• the frequent use of enemas (such as coffee enemas or high colonic washouts), as they can cause electrolyte imbalances.

### COST

It seems that many alternative therapies are inexpensive. In the study of Begbie et al, the median annual cost was $530. Almost two-thirds of women with advanced breast cancer using alternative therapies thought they were getting value for money. In the South Australian study, mean monthly expenditure on alternative therapies ranged from $1–$500, with a median of $10. Expenditure on alternative therapists was similar.

However, some therapies are remarkably expensive, with one woman spending $20,000 per year on alternative treatments. Conventional therapies are effectively subsidised by governments, and most patients do not pay the full cost of treatments. With alternative therapies, they are required to pay the full cost. Those using alternative therapies should be advised to enquire about costs before embarking on a course of alternative therapies, as they should with standard therapies.

### 9.3 DISCUSSING ALTERNATIVE THERAPIES

These three issues (effectiveness, safety and cost) need to be explored with all patients with advanced lung cancer who use alternative therapies. However, they can only be explored if the doctor is aware of the patient’s use of such therapies. Begbie et al found that 40% of women with cancer using alternative therapies did not tell their doctors about them. Presumably, those people were either not asked, or chose not to tell their doctors. It can be assumed that a negative attitude emanating from medical practitioners about alternative therapies would inhibit frank discussion. Such inhibition would mean patients would not learn of the medical practitioner’s support of, or concerns for, the way in which the alternative or complementary therapies may affect the conventional treatment patterns.
For many patients, feeling they can assume some control of the treatment of their disease is psychologically empowering. The physical problems that may arise from interference with conventional therapies may be attenuated by the strong psychological value of the alternative therapy. Conventional therapies often hold little hope of cure for patients, and it is understandable that patients will seek other solutions. Clinicians should also be aware that decisions to use alternative therapies might not be based on the same philosophical approach as that used by doctors.

It is to everyone’s advantage if patients are able to discuss alternative therapies openly, secure in the knowledge that they will continue to receive support and understanding from their doctors, whether or not those doctors agree with the therapy being used.

Due to lack of information relating to cancer of the lung, this chapter has been largely unchanged from *Clinical practice guidelines for the management of advanced breast cancer*, with permission of The National Breast Cancer Centre.

References


19. The Office of Complementary Medicines. 2003. PO Box 100, Woden Australian Capital Territory 2606, ph; 02 6232 8634, fax: 02 6232 8577, Therapeutic Goods Administration, Department of Health and Aged Care.


SECTION V
ECONOMIC CONSIDERATIONS

10. COST-EFFECTIVENESS

10.1 Economic burden of lung cancer in Australia

10.2 Role of economic evidence in the development of the guidelines

- Smoking cessation and prevention
  - Interventions provided by health care professionals
  - Generic and personalised self-help material
  - Nicotine replacement therapy (NRT)
  - Mass media and other anti-smoking campaigns
  - Intervention for hospitalised patients
  - Other pharmacological therapies including bupropion

- Screening
  - Initial assessment and follow-up
  - Use of positron emission tomography in staging of NSCLC

- Treatment of NSCLC
  - Follow-up after surgical management
  - Chemotherapy for advanced (Stage IIIB & IV) NSCLC
  - Radiotherapy and combination therapies

- Treatment of SCLC
10.1 ECONOMIC BURDEN OF LUNG CANCER IN AUSTRALIA

In 1996 lung cancer was the second most common malignant cancer in males and fourth most common in females\(^1\). Surgical resection provides curative therapy for early stage cancer, with five-year survival rates for early stage non-small cell lung cancer (NSCLC) ranging from 25\%–67\%. However, less than 20\% of lung cancers are diagnosed when the cancer is still localized\(^2\) and there are limited options for treatment of disseminated lung cancer. These factors have resulted in lung cancer being the most common cause of cancer death in males and the second most common in females\(^3\). In NSW the five year relative survival rates for lung cancer was the lowest of any cancer, at 10\% for males and 12\% for females, between 1980 and 1995\(^4\).

The estimated burden of disease attributable to lung cancer in Australia is outlined in Table 1–10. Years of Life Lost (YLL) due to lung cancer are considerably higher than Years Lost due to Disability (YLD). This reflects the fact that the ‘burden of cancer is dominated by mortality rather than lengthy periods of disability’\(^4\).

| Table 1–10 Burden of disease attributable to lung cancer in Australia, 1996\(^4\) |
|----------------------------------|-----------------|-----------------|-----------------|
|                                  | Total           | Males           | Females         |
|                                  | Number          | Per cent        | Number          | Per cent        | Number          | Per cent        |
| Deaths                           | 7,307           | 5.7             | 5,090           | 7.5             | 2,217           | 3.6             |
| YLL                              | 83,146          | 6.1             | 55,030          | 7.3             | 28,117          | 4.7             |
| YLD                              | 7,375           | 0.6             | 4,970           | 0.1             | 2,405           | 0.5             |
| DALY                             | 90,522          | 3.6             | 60,000          | 4.5             | 30,521          | 2.6             |

Abbreviations: YLL = Years of Life lost; YLD = Years Lost due to Disability; DALY = Disability Adjusted Life Year

The Australian Institute of Health and Welfare have estimated the costs of lung cancer at a macro level. In 1993–94 lung cancer was estimated to account for 5.6\% of total health care system costs in Australia. It ranked fifth in terms of the most ‘expensive’ cancers in Australia with total health care expenditure on lung cancer estimated at $107 million in 1993–94 (this estimate includes hospital, medical, pharmaceuticals, nursing home and allied health services, public health programs, research, other institutional and non-institutional and administration expenditure\(^4\)). Lung cancer ranks as the third most costly cancer for males aged 45–64 and the fourth most costly cancer for males and females aged over 65\(^5\). Total treatment costs for per case of lung cancer were estimated at $14,298 in 1993–94, which ranks twelfth in terms of the most costly cancer to treat\(^6\). However, there is relatively little micro-level information available in Australia about treatment patterns and resource use for lung cancer, particularly in terms of resource use by stage at diagnosis.
10.2 ROLE OF ECONOMIC EVIDENCE IN THE DEVELOPMENT OF GUIDELINES

The NHMRC has identified two main areas where economic evidence is important in the development of clinical practice guidelines:

• determination of which treatment alternatives are the most cost-effective
• determination of whether a proposed clinical practice guideline is cost-effective.

In the development of these guidelines, the emphasis has been in the first instance on identifying those interventions for which there is evidence of effectiveness, before addressing questions of cost-effectiveness. There is limited evidence available within Australia to assess the costs and cost-effectiveness of alternatives for management of lung cancer. However, there is a range of international literature that provides information about the relative cost-effectiveness of alternatives, and this information can be used to inform the development of these guidelines.

The approach taken in reviewing the economic evidence involved:

• identifying those areas where economic evidence is likely to be important
• identifying those areas where economic evaluation evidence is available
• reviewing and summarising the economic evaluation literature.

However, it is important to note that international economic evaluation literature is limited in its relevance to Australia because of differences in cost structures and reimbursement arrangements, and because the comparator in international studies may not reflect current practice in Australia.

A search was conducted using the databases Medline and Embase, covering the period 1993–2002. Economic evaluation literature that pre-dates 1993 was considered to be of limited relevance because of changes in technology, cost structures and management practices. The key words included lung cancer, economic evaluation, cost-effectiveness analysis, cost benefit analysis, cost analysis and cost. Articles were included if they were economic evaluations, that is, if they involved comparison of alternative interventions in terms of costs and consequences. A supplementary search was undertaken to identify economic evaluations of smoking cessation interventions. Articles were classified into seven main areas:

• smoking cessation and prevention
• screening
• initial assessment and follow-up
• lung cancer imaging including the use of PET
• treatment of non-small cell lung cancer (NSCLC)
• treatment of small cell lung cancer (SCLC)
• radon exposure (environmental exposure)(see Appendix 5).

These groupings reflected the main areas in which economic evaluation of interventions have been undertaken.
Articles were reviewed using the criteria recommended in the *How to compare the costs and benefits: evaluation of the economic evidence*. The shadow price criteria in this document were used as a basis for assessing the relative cost-effectiveness of interventions. That is,

- interventions that fall below the threshold of $30,000 per life-year saved (LYS) are considered to be relatively cost-effective (good value for money) and can be recommended
- interventions that exceed a threshold of $100,000 per LYS are considered not to be cost-effective and cannot be recommended without a strong justification
- interventions that fall between $30,000 per LYS and $100,000 per LYS require further consideration.

However, assessment of overseas economic evaluations and even some Australian economic evaluations in these terms should be treated with some caution. Whether these costs and outcomes would be realised if the intervention were adopted in the Australian context depends upon a number of factors, but particularly on whether the comparator for the study reflects current practice in Australia.

Cost-effectiveness results from studies are presented as reported in the relevant studies (that is, in the currency and time period as reported in the study), but also, for comparative purposes, converted to 2001 Australian dollars. Results in terms of 2001 Australian dollars are reported in parentheses. The conversion was undertaken using the OECD purchasing power parity estimates (http://www.oecd.org/std/ppp/) for the relevant year of the study to convert to Australian dollars for that year, then using the Australian Bureau of Statistics Health Price Index (weighted average of eight capital cities; ABS, 2002; Consumer Price Index Catalogue 6401.0) to convert the relevant costs to 2001 Australian dollars. Results in terms of 2001 Australian dollars are reported in parentheses below. However, in comparing across studies it should be noted that the results from different studies are not directly comparable. In particular, the scope of the studies may differ in terms of the range of costs and consequences considered, the perspective of the study and the choice of comparator. In addition, particularly for earlier studies, there may be important changes in cost structures and technology that limit comparability. The indicative cost-effectiveness estimates in 2001 Australian dollars should be treated as providing a guide to the likely cost-effectiveness of the interventions in the Australian setting, given the shadow prices suggested above.

The findings of the literature review are summarised below.
SMOKING CESSATION AND PREVENTION

A number of studies have been undertaken to assess the cost-effectiveness of various smoking cessation interventions, including:

- nicotine replacement therapy and other pharmacological therapies
- information programs and ‘Quit smoking’ campaigns delivered through various avenues (e.g. GP, pharmacist, community, media)
- counselling programs (e.g. group therapy and individual therapy)
- intervention on hospital admission.

In general cost-effectiveness studies of smoking cessation do not directly assess the potential impacts on lung cancer morbidity and mortality, and many studies report results in terms of intermediate outcome measures such as additional quitters. This is partly because of the number of additional assumptions required to extrapolate from additional quitters/non-smokers to impact on morbidity and mortality. However, given the importance of smoking as a risk factor for lung cancer, it is valuable to consider the cost-effectiveness of interventions aimed at reducing or preventing smoking.

In general, the cost-effectiveness research undertaken on smoking cessation and prevention indicates that smoking interventions represent good value for money. These results are primarily because of the relatively high level of benefits generated from the potential to avert years of life lost through reductions in morbidity and mortality, as well as because many of the interventions are relatively low cost compared with other health care interventions. Cost-effectiveness results do vary considerably between interventions. However, it is difficult to directly compare cost-effectiveness estimates across studies as estimates reflect not only the costs and effects of the alternative therapies but also different assumptions concerning the range of costs and benefits that are included in the evaluation.

INTERVENTIONS PROVIDED BY HEALTH CARE PROFESSIONALS

Smoking interventions can be delivered through a number of health care professionals including general practitioners, nurses, pharmacists and counsellors. There has been little cost-effectiveness research on this issue. Buck, Richmond et al evaluated the cost-effectiveness of a GP delivered smoking cessation intervention known as Smokescreen, which involves GP training. The cost-effectiveness of this intervention was estimated at $183 (A$208) per additional abstainer. Viney, Haas et al compared a number of different strategies including a GP based brief advice intervention and a more structured intervention consisting of a number of sessions. The brief advice approach was found to be more cost-effective at $6–$41 per quitter ($A7–$50).

Two studies have evaluated the cost-effectiveness of pharmacist intervention to assist smoking cessation. Cost-effectiveness estimates range from £300 (A$672) per one additional quit for pharmacists who were trained to provide ‘more
appropriate’ information to people looking to stop smoking\(^9\) to £509.60 (A$1051) for a program which consisted of a ‘contract’ between the pharmacist and patient and a series of counselling sessions over a 6 month period\(^10\).

Counsellors provide another avenue through which smoking interventions can be delivered. The Mayo Clinic Nicotine Dependence Center (USA) provides a counselling service, which consists of an initial consultation and the formulation of an individual treatment plan, which may include group therapy, inpatient program and/or pharmacologic therapy. Croghan, Offord et al\(^11\) evaluated this program and estimated a net cost per life-year gained of $6828 (A$11 693). Prathiba, Tjeder et al\(^12\) evaluated the cost-effectiveness of a counselling programme provided to hospital in-patients and out-patients. They estimated the cost per life-year saved from such a program at £340–£426 (A$667–$836), and the cost of an additional quit was valued at £851 (A$1671).

These results indicate that appropriately trained health care professionals may be able to provide a cost-effective method through which to disseminate information on smoking cessation and/or conduct ‘quit smoking’ campaigns. However, more evidence is needed to make a recommendation.

**GENERIC AND PERSONALISED SELF-HELP MATERIAL**

One study, by Lennox, Osman et al\(^13\), was found to have looked at the cost-effectiveness of generic versus tailored self-help material. This study evaluated the impact of computer tailored and non-tailored smoking cessation letters and found that the tailored letter did not increase cessation rates over and above that of the non-tailored letter. However, it was found to be effective in promoting a shift towards smoking cessation. The cost-effectiveness of the non-tailored letter (compared to no letter) was valued at £37 (A$49) per quitter, with the cost per life-year gained valued £50–£122 (A$67–$163). This study suggests that letter writing (either tailored or not tailored) is a cost-effective method of getting patients to quit smoking. However, non-tailored letter writing appears to be more cost-effective than tailored letter writing.

**NICOTINE REPLACEMENT THERAPY (NRT)**

Four studies were found which evaluated the cost-effectiveness of nicotine patches and one study evaluated the cost-effectiveness of Nicorette nasal spray. In all studies the incremental cost-effectiveness of nicotine patch or spray therapy was compared with (some form of) counselling alone. As outcome measures varied from study to study, the results have been set out in Table 2–10 (overleaf).

In all studies nicotine replacement therapy, when used as an adjunct to counselling, was found to be a cost-effective intervention. Therefore, there appears to be support for recommending the use of nicotine replacement therapy in combination with counselling services.
MASS MEDIA AND OTHER ANTI-SMOKING CAMPAIGNS

Anti-smoking campaigns and media campaigns have taken many forms including mass media campaigns, community programs and work-site smoking cessation programs. Cost-effectiveness studies have been undertaken to evaluate a handful of these campaigns.

Relative to other programs mass media campaigns appear to be relatively cost-effective. However, there is insufficient evidence to recommend one ‘type’ of campaign over another.

Table 2–10 Summary of NRT cost-effectiveness literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Study country</th>
<th>Comparator</th>
<th>Unit of benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akehurst and Piercy 1994¹⁴</td>
<td>UK</td>
<td>GP counselling alone versus GP counselling and nicotine patch therapy</td>
<td>Cost-effectiveness per quitter is £3 074 (A$8 264)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Marginal cost per quitter was £1 252 (A$3 365), marginal cost per death avoided £58 894 (A$158 336) and marginal cost per life-year gained £4 526 (A$12 341).</td>
</tr>
<tr>
<td>Akehurst and Piercy 1994¹⁵</td>
<td>UK</td>
<td>GP counselling alone versus GP counselling and nicotine nasal spray</td>
<td>Cost per life-year saved £1430 (A$3 844).</td>
</tr>
<tr>
<td>Fiscella and Franks 1996¹⁶</td>
<td>USA</td>
<td>GP counselling alone versus GP counselling and nicotine patch therapy</td>
<td>Cost of 1 additional lifetime quitter $7 332 (A$10 745)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incremental cost-effectiveness ranged $4 930–$10 043 (A$7 225–$14 718) per QALY for males and $4 955–$6 983 (A$7 262–$10 234) per female.</td>
</tr>
<tr>
<td>Stapleton, Lowin et al 1999¹⁷</td>
<td>UK</td>
<td>GP counselling alone versus GP counselling and nicotine patch therapy</td>
<td>Incremental cost per life-year saved range £395–£785 (A$775–$1 541).</td>
</tr>
</tbody>
</table>
Table 2–10  Summary of NRT cost-effectiveness literature (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study country</th>
<th>Comparator</th>
<th>Unit of benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasley, McNagny et al 1997&lt;sup&gt;18&lt;/sup&gt;</td>
<td>USA</td>
<td>Counselling alone versus GP counselling and nicotine patch therapy</td>
<td>Average cost per life-year saved: $965–$1 585 (A$1 414–$2 322) for males; $1 634–$2 360 (A$2 394–$3 459) for females</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incremental cost per life-year saved: $1 796–$2 949 (A$2 632–$3 322) for males; $3 040–$4 391 (A$4 455–$6 435) for females</td>
</tr>
</tbody>
</table>

Table 3–10  Summary of mass media and other anti-smoking campaigns cost-effectiveness literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Study country</th>
<th>Intervention type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mudde and DeVries 1999&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Netherlands</td>
<td>Mass media</td>
<td>US$12 per quit (A$17).</td>
</tr>
<tr>
<td>Tillgren, Rosen et al 1993&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Sweden</td>
<td>Quit and win contest</td>
<td>US$188–$1 222 (A$342–$2 223) per life-year saved.</td>
</tr>
<tr>
<td>Tengs, Osgood et al 2001&lt;sup&gt;23&lt;/sup&gt;</td>
<td>USA</td>
<td>National school based education program</td>
<td>$4 900–$34 000 (A$6 826–$47 356) per quality adjusted life-year.</td>
</tr>
<tr>
<td>Viney, Haas et al 1996&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Australia</td>
<td>Mass media</td>
<td>$11–$30 per quitter (A$13–$36)</td>
</tr>
</tbody>
</table>
INTERVENTION FOR HOSPITALISED PATIENTS

Two studies were found which attempted to evaluate the cost-effectiveness of a hospital based smoking cessation interventions. Meenan, Stevens et al\textsuperscript{25} estimated that the incremental cost per incremental quit at $3697 (A$5975) and the incremental discounted life-year saved ranged between $1691 (A$2733) and $7444 (A$12 031). This study provides some evidence that smoking cessation interventions for hospital in-patients may be cost-effective. However, more evidence is required.

OTHER PHARMACOLOGICAL THERAPIES INCLUDING BUPROPION

Nielsen and Fiore\textsuperscript{26} conducted a cost benefit analysis of bupropion, nicotine transdermal patch (NTP) and a combination of the two therapies. This study found that bupropion alone, with a net benefit estimated at $338 (A$428), had a greater net benefit than either NTP at $26 (A$33), combination therapy at $178 (A$226) or placebo at $258 (A$327). Johnson, Lucas et al\textsuperscript{27} also compared the cost-effectiveness of NTP against bupropion SR, and found that, despite similar effectiveness levels, bupropion SR was more cost-effective than NTP. The cost-effectiveness of bupropion hydrochloride as part of a health plan and work-site smoking cessation program was also evaluated and estimated to have a cost-benefit ratio of $1:4.10–$4.69 (A$1.30:5.33–6.09)\textsuperscript{28}.

These studies indicate that bupropion is a cost-effective intervention for smoking cessation and may be more cost-effective than nicotine replacement therapy. However, the number of studies is limited.

SCREENING

The prevailing consensus appears to be that mass screening programs to detect lung cancer are of doubtful cost-effectiveness. This is largely driven by relatively low rates of detection accuracy of plain chest x-rays. Estimates of cost-effectiveness for mass screening with plain chest x-rays vary from $9000 (A$11 414) per undiscounted life-year gained\textsuperscript{29} to $93 000 (A$120 834)\textsuperscript{30} per life saved. These estimates would appear to provide some support for mass screening. The former study assumes an 18% reduction in mortality, based on extrapolation of staging data from four randomised controlled trials, and assuming a 100% participation rate in annual screening of male smokers aged 45–80. However, the assumption of an 18% reduction in mortality is not adequately supported, given that trials on which the evidence was based did not show a mortality benefit. A further limitation is that consequences are not discounted. The latter study is a decision analytic model, with the detection rate based on results from a mass screening program in Japan. Both studies depend on the assumptions about detection rates, and the impact of early detection on survival.
The paucity of recent studies and the continued debate about whether plain x-rays are sensitive enough to detect lung cancer at a stage early enough to undertake curative treatment means that there does not appear to be strong support for recommending mass screening programs with plain x-rays on the basis of cost-effectiveness evidence.

Recent technological advances, primarily the development of CT screening, have led to improvements in the sensitivity of screening. Marshall, Simpson\textsuperscript{31,32} and Okamoto\textsuperscript{33} have evaluated the cost-effectiveness of CT screening for lung cancer. Marshall, Simpson\textsuperscript{32} developed a decision analytic model to examine the cost-effectiveness of annual lung cancer screening based on CT for a high-risk cohort aged 60–74, combining data from the ELCAP project and the SEER registry. The model assumes that screening will shift the stage distribution at diagnosis. Based on this the cost per life-year saved is $19,000 ($A26,500), but in sensitivity analysis, this varied to $60,000 ($A85,000) per LYS. The same authors have used similar data to examine the cost-effectiveness of one-time screening and have estimated that the cost per life-year saved ranges from $5940 ($A8275) for a very high-risk cohort (lung cancer prevalence of 2.7%) to $23,100 ($A32,200) per life-year saved for a lower risk population of smokers. Okamoto\textsuperscript{33} used a decision analytic model to examine the cost-effectiveness of CT screening compared with the current x-ray based screening in Japan, and concluded that while CT screening would be more expensive, it would also be more effective.

Despite the fact that CT screening is more expensive than screening by plain x-rays, the preliminary evidence suggests that the improvements in detection provided by CT scanning may outweigh the additional costs, leading to better estimates of cost-effectiveness for lung cancer screening. A major limitation of these studies is that the impact on mortality is based on extrapolation from screening results to a survival benefit. However, at this stage survival benefits from screening have not been demonstrated. Therefore, these cost-effectiveness estimates should be viewed with some caution as they are based on limited data on the effectiveness of CT screening, and may change with further evidence from randomised controlled trials. In general, the studies indicate that improvements in scanning technology that lead to better diagnostic accuracy (without parallel increases in cost) will improve the cost effectiveness of screening programs. For all screening programs, plain x-ray and CT, cost-effectiveness is significantly improved when screening is targeted at high-risk groups.
Table 4–10  Summary of screening cost-effectiveness literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Study country</th>
<th>Screening type</th>
<th>Unit of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baba, Takahashi et al 1998</td>
<td>Japan</td>
<td>Plain x-ray</td>
<td>Cost of a life saved ~$93 000 (A$117 942).</td>
</tr>
<tr>
<td>Caro, Klittich et al 2000</td>
<td>USA</td>
<td>X-ray</td>
<td>Cost-effectiveness of $9 000 (A$11 413) per undiscounted life-year gained or less than $20 000 (A$25 364) per discounted life-year gained.</td>
</tr>
<tr>
<td>Chirikos et al 2002</td>
<td>USA</td>
<td>CT scan</td>
<td>Incremental cost per life-year ratio $33 557 (A$45 789)–$90 022 (A$122 835).</td>
</tr>
<tr>
<td>Marshall, Simpson 2001</td>
<td>USA</td>
<td>CT scan</td>
<td>High-risk cohort cost ~$19 000 (A$26 469) per life-year saved. ($10 800–$62 000 [A$15 045–$86 372])</td>
</tr>
<tr>
<td>Marshall, Simpson 2001</td>
<td>USA</td>
<td>CT scan</td>
<td>High-risk cohort one time screen is $5 940 (A$8 275) per life-year saved. General population $23 100 (A$32 180) per life-year saved.</td>
</tr>
</tbody>
</table>

INITIAL ASSESSMENT AND FOLLOW-UP

There have been relatively few papers assessing the economic evidence for approaches to initial assessment of patients with suspected lung cancer. Raab, Hornberger et al evaluated the cost-effectiveness of sputum cytology, when used as the first test preceding all other tests, in the diagnosis of lung cancer. Testing sputum cytology was found to be the dominant strategy as it lowered both medical costs and mortality risk. This study indicates that sputum cytology may provide a cost-effective option in the diagnosis of lung cancer. However, recommendations cannot be based on the findings on only one study. Therefore, this study can be taken as indicative of potential cost savings with further research required.

The Canadian Lung Oncology Group have investigated the costs and outcomes of investigation for mediastinal disease for patients with apparently operable lung cancer, comparing mediastinoscopy with CT. They concluded that CT is likely to produce the same number or fewer unnecessary thoracotomies, and be less costly.
In a more recent study, the Canadian Lung Oncology Group have also undertaken a randomised controlled trial and comparison of costs of a limited and a full investigation strategy prior to the final decision regarding surgery. In the limited strategy patients underwent CT of the chest and mediastinoscopy, and proceeded to thoracotomy if there was no evidence of major mediastinal disease on CT, mediastinoscopy or both. In the full investigation strategy, patients also underwent bone scintigraphy and CT of the chest, liver, adrenal glands and head after mediastinoscopy. Patients in the full investigation group were less likely to have a thoracotomy, but there was no significant difference in the relative risk of thoracotomy without cure between the two strategies. While the full investigation strategy had higher costs associated with professional fees, overall, the average cost of full investigation was lower than for the limited strategy, because of costs of hospital episodes avoided. However, the difference in costs was not significant.

USE OF POSITRON EMISSION TOMOGRAPHY IN STAGING OF NSCLC

A number of studies have used decision analytic models to evaluate the cost-effectiveness of the use of Positron Emission Tomography (PET), in general FDG-PET, in staging and management of NSCLC. PET has been considered as both an adjunct and an alternative to conventional staging, which in most studies is assumed to be CT scanning. Most studies provide preliminary evidence to suggest that PET may be relatively cost-effective because of the potential to avoid unnecessary surgery through more accurate staging, and particularly through detection of disseminated disease. For example, Valk, Pounds et al\(^{38}\) and von Schulthess, Steinert et al\(^{39}\) both took a cost-minimisation approach and estimated that PET would be cost-saving as an adjunct or an alternative to conventional staging involving CT. However, neither study examines the impact on mortality, particularly the potential for PET to result in surgery avoided for potentially curable patients.

Dietlein, Weber et al\(^{40}\) and Scott, Shepherd et al\(^{41}\) examined the relative cost-effectiveness of a number of different potential strategies for incorporating PET in staging of NSCLC. Dietlein, Weber et al\(^{40}\) concluded that PET was likely to be cost-effective (143 EUR/LYS) for patients with normal sized mediastinal lymph nodes when used as an adjunct to conventional staging. The results of Scott, Shepherd et al\(^{41}\), suggest that PET is less cost-effective, but may be good value for money under some strategies, particularly for patients who had no mediastinal lymph node involvement on CT.

These results suggest that the cost-effectiveness of PET depends on how it is used in relation to conventional staging, and on the accuracy of the initial staging. The limitation of all the current cost-effectiveness analyses of PET is that they rely on estimates of sensitivity and specificity of PET based on relatively small case series rather than randomised controlled trials. Further, the relative cost-effectiveness of PET depends critically on the management decision made based on the PET results (that is, whether thoracotomy will be avoided, or whether the patient will have other...
treatment such as chemotherapy, as an addition or alternative to thoracotomy)\textsuperscript{42}. Thus, it is important to assess the cost-effectiveness of PET in the local context and using evidence from randomised controlled trials. Two recent studies provide new evidence that will be critical in determining the value of PET in management of NSCLC. van Tinenen, Hoekstra et al\textsuperscript{43} have undertaken a randomised controlled trial of pre-operative assessment of patients with suspected Stage I-III NSCLC. Their results suggest that PET may avoid thoracotomy in 20\% of patients. Although they have not as yet reported cost-effectiveness analysis, these results suggest that PET may be relatively cost-effective. However, preliminary cost-effectiveness results from another randomised controlled trial and cost-effectiveness analysis\textsuperscript{44} suggest that PET may not be cost-effective in management of Stage I–II NSCLC.

**TREATMENT OF NON-SMALL CELL LUNG CANCER (NSCLC)**

There is relatively limited information about the cost-effectiveness of the range of treatments for non-small cell lung cancer, including the value of surgery for potentially operable disease, the appropriateness of adjuvant therapy and the appropriate choice of chemotherapy agent for disseminated cancer.

**FOLLOW UP AFTER SURGICAL MANAGEMENT**

There is very little information on cost-effectiveness of alternative follow-up strategies. Younes, Gross et al\textsuperscript{45} compared the cost-effectiveness of a strict follow-up regime (consisting of strict visits, imaging and laboratory examinations) with infrequent visits. The study found that, for patients with resected NSCLC, the strict follow-up strategy was more expensive but did not lead to a significant difference in interval between recurrence.

Gilbert, Reid et al\textsuperscript{46} evaluated whether follow-up by a thoracic surgeon after cancer resection, as opposed to a GP, altered survival. The cost per recurrence detected by a thoracic surgeon was $4367 (A$5108) compared with $1105 (A$1293) for the cost per recurrence detected by a GP. No 5-year survival benefit for surgeon-detected recurrences was found. Therefore, follow-up via a GP was found to be relatively cost-effective.

Similarly, Egermann, Jaeggi et al\textsuperscript{47} examined the costs and outcomes of a strict protocol of regular follow-up for 10 years including clinic visits and chest radiography following resection for NSCLC, although it is not clear whether the comparator was no follow-up or a less frequent protocol. They concluded that the costs per life-year saved from the strict protocol were high.
CHEMOTHERAPY FOR ADVANCED (STAGE IIIB AND IV) NSCLC

A number of studies evaluating different chemotherapy regimes for advanced NSCLC have been undertaken since 1995, although there is considerable overlap between studies in terms of the modelling approaches used and the trial and other data used to estimate effectiveness. The results are summarised in Table 5–10.

In general, these studies, particularly the review studies, provide evidence that chemotherapy provides a small survival and quality of life gain that is relatively cost-effective compared with supportive care\(^*\). The majority of these studies provide evidence to suggest that the incremental cost-effectiveness of some chemotherapy regimes is less than $A30 000 per life-year gained, although cost-effectiveness estimates vary considerably. However, there is insufficient evidence at this stage to recommend one particular chemotherapy agent or regime over others on the basis of cost-effectiveness. However, it should be noted that these results are sensitive to the method of estimating or extrapolating survival and quality of life data from trials, to the chemotherapy regimes, to the relative costs of different chemotherapy regimes, and to the method of delivery of chemotherapy, with inpatient care being more costly than outpatient care. While the studies provide evidence to suggest that some chemotherapy regimes appear to be relatively more cost-effective than others, and in some instances cost-saving, extrapolating these results to the Australian context is not appropriate, as the relative cost-effectiveness is largely driven by the relative costs of the different chemotherapy regimes and modes of delivery, which can vary internationally.
<table>
<thead>
<tr>
<th>Studies</th>
<th>Study country</th>
<th>Study questions</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer and Brandt 1996</td>
<td>Italy</td>
<td>Comparison of 4 cisplatin regimens: G+P; MIP; E+P; NVB+P</td>
<td>No significant difference in survival Based on $/tumour response, gemcitabine &amp; cisplatin is more cost-effective</td>
</tr>
<tr>
<td>Will, Berthelot et al 2001</td>
<td>Canada†</td>
<td>Comparisons of a range of chemotherapy regimes with best supportive care (BSC) including VLB+P; NVB; NVB+P; PAX+P (3 doses); G</td>
<td>VLB+P dominates BSC Incremental cost of chemotherapy compared with BSC ranges from $1 900–$27 000/LYS ($A2 353–33 447); $2 658–$37 841/QALY ($A3 300–$46 300) At a threshold of $A30 000/QALY, preferred regime is NVB+P; for lower thresholds VLB+P is preferred, for higher; G is preferred; Results vary if outcome measure is LYS</td>
</tr>
<tr>
<td>Koch, Johnson et al 1995</td>
<td>Germany</td>
<td>Comparison of gemcitabine versus ifosfamide/etoposide; assumes equal efficacy</td>
<td>Gemcitabine has the potential to be cost saving</td>
</tr>
<tr>
<td>Clegg, Scott et al 2002</td>
<td>UK</td>
<td>Comparison of a range of chemotherapy regimens with BSC: G; G+P; NVB; NVB+P; PAX; PAX+P– various doses; DOC; DOC 2nd line</td>
<td>Incremental cost compared with BSC varied from £4 091 ($A8 633) for NVB to £46 610 ($A98 360) for PAX. At a threshold of $A30 000/LYS NVB; NVB+P; G; G+P; and PAX+P cost-effective</td>
</tr>
<tr>
<td>Studies</td>
<td>Study country</td>
<td>Study questions</td>
<td>Conclusions</td>
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<td>-------------------------</td>
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</tr>
<tr>
<td>Annemans, Giaccone et al 1999&lt;sup&gt;54&lt;/sup&gt;</td>
<td>The Netherlands, Belgium, Spain and France</td>
<td>Comparison of paclitaxel &amp; cisplatin versus teniposide &amp; cisplatin for advanced NSCLC</td>
<td>Trial results show no difference in survival or quality of life. PAX+P more expensive but additional responders. Not clear that all costs were considered.</td>
</tr>
<tr>
<td>Smith, Hillner et al 1995&lt;sup&gt;55&lt;/sup&gt;</td>
<td>USA</td>
<td>Comparison of three chemotherapy regimes: NVB; NVB+P; VIN+P</td>
<td>Incremental $/LYS ranged from $15 500 (NVB+P versus VIN+P) to $22 100 (VIN+P versus NVB alone). ($A23 000–$33 000).</td>
</tr>
<tr>
<td>Hillner and Smith 1996&lt;sup&gt;56&lt;/sup&gt;, 1998&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Canada†</td>
<td>Comparison of chemotherapy regimes with BSC: NVB alone, NVP+P; VIN+P; VP-16-P; VLB+P</td>
<td>NVB alone; NVB+P (delivered in outpatient setting); VLB+P and VP-16-P are dominant. Cost per LYS for other therapies less than $A20 000.</td>
</tr>
<tr>
<td>Evans and Le Chevalier 1996&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Canada†</td>
<td>Comparison of gemcitabine with BSC. Incremental $/LYS</td>
<td>Incremental $/LYS $630–$1 623 0 depending on assumptions and numbers of cycles ($A854–$22 007).</td>
</tr>
<tr>
<td>Evans 1998&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Canada†</td>
<td>Comparison of gemcitabine with BSC. Incremental $/LYS</td>
<td>Incremental $/LYS $76 370–$1 38 578 based on trial protocol ($A84 451–$1 53 242).</td>
</tr>
<tr>
<td>Earle and Evans 1999&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Canada†</td>
<td>Comparison of PAC+P with standard E+P for advanced NSCLC</td>
<td>Outpatient protocol incremental $/LYS 30 619 ($A33 000).</td>
</tr>
</tbody>
</table>
Table 5–10  Results of studies investigating costs and outcomes of alternative chemotherapy regimens (continued)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study country</th>
<th>Study questions</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leighl, Shepherd et al 2002</td>
<td>Canada</td>
<td>Comparison of 2nd line docetaxel with BSC based on the TAX 317 trial</td>
<td>Incremental $/LYS ranged from $31 776–$57 749 ($A37 168–$67 548), but results were sensitive to changes in survival estimates, increasing to $117 434 ($A137 362)</td>
</tr>
<tr>
<td>Sacristan, Kennedy-Martin 2002</td>
<td>Spain</td>
<td>Comparison of G+P with E+P</td>
<td>No differences in survival were found; Gem+P was lower cost and had higher response rate and longer time to progress. Preferred on a cost-minimisation basis</td>
</tr>
<tr>
<td>Ramsey, Moinpour et al 2002</td>
<td>USA</td>
<td>Comparison of NVP+P with PAX+P</td>
<td>No difference in survival or cancer related quality of life; NVB+P less costly; preferred on a cost-minimisation basis</td>
</tr>
<tr>
<td>Earle and Evans 1997</td>
<td>Canada†</td>
<td>Comparison of PAC alone with BSC</td>
<td>Incremental Cost per LYS varied from $4 778–$21 377 depending on assumptions ($A6 428–$28 986)</td>
</tr>
<tr>
<td>Rubio-Terres, Tisaiere et al 2002</td>
<td>Spain</td>
<td>Comparison of DOC+P; PAX+P; PAX+C</td>
<td>No difference in survival; Doc+P less costly; preferred on cost-minimisation basis</td>
</tr>
</tbody>
</table>

†POHEM is a population health micro-simulation model developed by Statistics Canada, which is used to evaluate interventions. The lung cancer model was developed in collaboration with oncologists at the Ottawa Regional Cancer Centre (ORCC).

Abbreviations: BSC: best supportive care; DOC: docetaxel; DOC+P: docetaxel & cisplatin; E+P: etoposide & cisplatin; G: gemcitabine; G+P: gemcitabine & cisplatin; MIC: MIP: mitomycin, ifosfamide & cisplatin; NVB: vinorelbine; NVB+P: vinorelbine & cisplatin; NVP+P; PAX: paclitaxel; PAX+C: paclitaxel & carboplatin; PAX+P: paclitaxel & cisplatin; T+P: teniposide & cisplatin; VIN+P: vindesine & cisplatin; VLB+P: vinblastine & cisplatin; VP-16-P
RADIOThERAPY AND COMBINATION THERAPIES

Coy, Schaufsma et al.\(^6\) has estimated the incremental cost per LYS and cost per QALY for high dose palliative radiotherapy for advanced NSCLC compared with BSC to be $12,253 per LYS ($A13,500) and $17,012 per QALY ($A18,900). However, this study was not based on trial data and the results were sensitive to assumptions about cost and survival benefit.

Evans, Will et al.\(^6\) have used the Canadian POHEM model to examine the cost-effectiveness of combined modality interventions (pre and post operative chemotherapy and pre and post operative chemotherapy and radiotherapy) for Stage III NSCLC. They estimate that the cost per LYS ranges from $3,348–$14,958 ($A4,500–$20,300) for Stages IIIA and IIIB cancer, and may be lower with outpatient therapy. However, again, these results are not based on trial data and are sensitive to estimates of cost and survival gain.

TREATMENT OF SMALL CELL LUNG CANCER (SCLC)

The cost-effectiveness literature with regards to the treatment of small cell lung cancer is sparse, with only 5 articles located. Four studies evaluated alternative chemotherapy options including: preemptive administration of G-CSF for patients treated with conventional myelosuppressive cytotoxic chemotherapy, routine use of granulocyte colony stimulating factor, cisplatin in combination with either etoposide or etoposide phosphate, and oral versus intravenous etoposide. A further study on the effectiveness of prophylactic cranial irradiation was also reviewed.

As each study tackles a different treatment question it is difficult to draw conclusions or make any recommendations from the available literature. At best, these studies provide an initial indication of possible cost-effectiveness for certain treatment options.

References


6. NHMRC: How to compare the costs and benefits: evaluation of the economic evidence. 2001


44. Boyer M, Viney R, Fulham M, et al: A randomised trial of conventional staging (CS) with or without positron emission tomography (PET) in patients with Stage 1 or 2 Non-Small Cell Lung Cancer. 2001


59. Evans WK: Cost-effectiveness of vinorelbine alone or vinorelbine plus cisplatin for stage IV NSCLC. Oncology (Huntington) 12:18–25, 1998

60. Evans WK: An estimate of the cost effectiveness of gemcitabine in stage IV non-small cell lung cancer. Seminars in Oncology 23:82–9, 1996


APPENDIX 1 – TNM STAGING


LUNG TUMOURS

INTRODUCTORY NOTES

Each site is described under the following headings:

- Rules for classification with the procedures for assessing T, N and M categories; additional methods may be used when they enhance the accuracy of appraisal before treatment
- Anatomical subsites where appropriate
- Definition of the regional lymph nodes
- TNM Clinical classification
- pTNM Pathological classification
- G Histopathological grading where applicable
- Stage grouping
- Summary

REGIONAL LYMPH NODES

Direct extension of the primary tumour into lymph nodes is classified as lymph node metastasis.
DISTANT METASTASIS

The categories M1 and pM1 may be further specified according to the following notation:

| Pulmonary | PUL | Bone marrow | MAR |
| Osseous   | OSS | Pleura       | PLE |
| Hepatic   | HEP | Peritoneum   | PER |
| Brain     | BRA | Adrenals     | ADR |
| Lymph nodes | LYM | Skin         | SKI |
| Others    | OTH | Others       | OTH |

R CLASSIFICATION

The absence or presence of residual tumour after treatment is described by the symbol R. The definitions of the R classification are:

RX  Presence of residual tumour cannot be assessed
R0  No residual tumour
R1  Microscopic residual tumour
R2  Macroscopic residual tumour
LUNG
(ICD-0 C34)

RULES FOR CLASSIFICATION
The classification applies only to carcinomas. There should be histological confirmation of the disease and division of cases by histological type.

The following are the procedures for assessing T, N and M categories:

- **T categories**: Physical examination, imaging, endoscopy, and/or surgical exploration
- **N categories**: Physical examination, imaging, endoscopy, and/or surgical exploration
- **M categories**: Physical examination, imaging, and/or surgical exploration

ANATOMICAL SUBSITES
1. Main bronchus (C34.0)
2. Upper lobe (C34.1)
3. Middle lobe (C34.2)
4. Lower lobe (C34.3)

REGIONAL LYMPH NODES
The regional lymph nodes are the intrathoracic, scalene and supraclavicular nodes.
TNM CLINICAL CLASSIFICATION

T - PRIMARY TUMOUR

TX  Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy

T0  No evidence of primary tumour

Tis  Carcinoma in situ

T1  Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie., not in the main bronchus)\(^1\)

T2  Tumour with any of the following features of size or extent:
   • More than 3 cm in greatest dimension
   • Involves main bronchus, 2 cm or more distal to the carina
   • Invades visceral pleura
   • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3  Tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

T4  Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina; separate tumour nodule(s) in the same lobe; tumour with malignant pleural effusion\(^2\)

Notes:

1  The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1.

2  Most pleural effusions with lung cancer are due to tumour. In a few patients, however, multiple cytopathological examinations of pleural fluid are negative for tumour, and the fluid is non-bloody and is not an exudate. Where these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as T1, T2 or T3.
N – REGIONAL LYMPH NODES

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M – DISTANT METASTASIS

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis, includes separate tumour nodule(s) in a different lobe (ipsilateral or contralateral)

PTNM PATHOLOGICAL CLASSIFICATION

The pT, pN, and pM categories correspond to the T, N, and M categories.

pN0 Histological examination of hilar and mediastinal lymphadenectomy specimen(s) will ordinarily include 6 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0.
**G HISTOPATHOLOGICAL GRADING**

GX  Grade of differentiation cannot be assessed
G1  Well differentiated
G2  Moderately differentiated
G3  Poorly differentiated
G4  Undifferentiated

**STAGE GROUPING**

<table>
<thead>
<tr>
<th>Occult carcinoma</th>
<th>TX</th>
<th>N0</th>
<th>M0</th>
</tr>
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<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T1, T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
### SUMMARY

**Lung**

<table>
<thead>
<tr>
<th>TX</th>
<th>Positive cytology only</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>$\leq 3 \text{ cm}$</td>
</tr>
<tr>
<td>T2</td>
<td>$&gt;3 \text{ cm}$, main bronchus $\geq 2 \text{ cm}$ from carina, invades visceral pleura, partial atelectasis</td>
</tr>
<tr>
<td>T3</td>
<td>Chest wall, diaphragm, pericardium, mediastinal pleura, main bronchus $&lt; 2 \text{ cm}$ from carina, total atelectasis</td>
</tr>
<tr>
<td>T4</td>
<td>Mediastinum, heart, great vessels, carina, trachea, oesophagus, vertebra; separate nodules in same lobe, malignant pleural effusion</td>
</tr>
</tbody>
</table>

| N1 | Ipsilateral peribronchial, ipsilateral hilar |
| N2 | Ipsilateral mediastinal, subcarinal |
| N3 | Contralateral mediastinal or hilar, scalene or supraclavicular |
| M1 | Includes separate nodule in different lobe |
LUNG

RULES FOR CLASSIFICATION

The classification applies to all types of carcinoma including small cell carcinoma. It does not apply to carcinoids.

**T Classification**

<table>
<thead>
<tr>
<th>Summary Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 &lt; 3 cm</td>
</tr>
<tr>
<td>T2 &gt;3 cm, main bronchus &gt; 2 cm from carina, invades visceral pleura, partial atelectasis</td>
</tr>
<tr>
<td>T3 Chest wall, diaphragm, pericardium, mediastinal pleura, Main bronchus &lt;2 cm from carina, total atelectasis</td>
</tr>
<tr>
<td>T4 Mediastinum, heart, great vessels, carina, trachea, oesophagus, vertebra; separate nodules in same node, malignant effusion</td>
</tr>
</tbody>
</table>

1. Tumour with local invasion of another lobe without tumour on the pleural surface should be classified as T2.
2. Invasion of phrenic nerve is classified as T3.
3. Vocal cord paralysis (resulting from invasion of the recurrent branch of the vagus nerve), superior vena caval obstruction or compression of the trachea or oesophagus is classified as T4.
4. T4 the “great vessels” are:
   - Aorta
   - Superior vena cava
   - Inferior vena cava
   - Main pulmonary artery (pulmonary trunk)
   - Intrapericardial portions of the right and left pulmonary artery
   - Intrapericardial portions of the superior and inferior right and left pulmonary veins

   Invasion of more distal branches does not qualify for classification as T4.
5. Direct extension to parietal pericardium is classified T3 and to visceral pericardium, T4.
6. Pleural effusion is classified as T4, unless there are multiple negative cytological examinations.
7. Tumour foci in the ipsilateral parietal and visceral pleura that are discontinuous from direct pleural invasion by the primary tumour are classified as T4.
8. Invasion of visceral pleura (T2) includes not only perforation of the mesothelium but also invasion of the lamina propria serosae.
9. Tumour extending to rib is classified as T3.
10. Pericardial effusion is classified the same as pleural effusion.
11. Multiple tumours of the same histological type in the same lobe is T4, but in different lobes is M1.
12. Multiple tumours of different histological type in the same lobe or in different lobes should be classified as T1-4 (m).

**M Classification**

Discontinuous tumours outside the parietal pleura in the chest wall or in the diaphragm are classified as M1.

**Small Cell Carcinoma**

The TNM classification and stage grouping should be applied to small cell carcinoma. TNM is of significance for prognosis of small cell carcinoma [21], and has the advantage of providing a uniform detailed classification of tumour spread. The former categories “limited” and “extensive” for small cell carcinoma have been inconsistently defined and used.

The category “limited disease” as used in Veterans’ Administration Lung Cancer Study Group system for classification of small cell carcinoma [15] corresponds to Stages I and III A to “extensive disease” to Stages III B (“extensive disease I”) and IV (“extensive disease II”).
APPENDIX 2 – MODIFIED STAGING FOR SMALL CELL LUNG CANCER

THE VETERANS' ADMINISTRATION LUNG STUDY GROUP (VALG) CLASSIFICATION

LIMITED DISEASE
(a) disease confined to one hemithorax, although local extensions may be present;
(b) no extrathoracic metastases except for possible ipsilateral, supraclavicular nodes if they can be included in the same (radiotherapy) portal as the primary tumour;
(c) primary tumour and regional nodes which can be adequately treated and totally encompassed in every (radiotherapy) portal.

EXTENSIVE DISEASE
Inoperable patients who cannot be classified as having limited disease.

CONSENSUS REPORT OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER (IASLC)

LIMITED DISEASE
‘Disease restricted to one hemithorax with regional lymph node metastases, including hilar, ipsilateral and contralateral mediastinal, and ipsilateral and contralateral supraclavicular nodes and should also include patients with ipsilateral pleural effusion independent of whether the cytology is positive or negative.’
EXTENSIVE DISEASE

‘All patients with sites of disease beyond the definition of limited disease.’

It is recommended that the IASLC revision of the VALG classification be used as it is independent of the subjective opinion of the radiation oncologist as to what can be ‘adequately treated and totally encompassed.’

References


APPENDIX 3 – PERFORMANCE STATUS CRITERIA OF THE EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG)\(^1\)

Performance status 0  Fully active, able to carry on all pre-disease activities without restriction.

Performance status 1  Ambulatory but restricted in physically strenuous activity. Able to carry out light work or sedentary work e.g. light housework, office work.

Performance status 2  Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about at least 50% of waking hours.

Performance status 3  Capable of only limited self-care, confined to bed or chair at least 50% of waking hours.

Performance status 4  Unable to carry on any self-care, totally confined to bed or chair.

Reference

Guidelines for managing lung cancer are by nature limited to what is known at a particular time, while new information becomes available continuously. In particular, new studies evaluating systemic treatments are increasingly being reported, and are likely to increase as new understandings of cancer biology are translated into new therapeutic targets. What follows is a survey of new randomised studies reported in the last 18 months that are likely to impact on systemic therapy options for treating non-small cell lung cancer. This is not a systematic review of all studies published or presented in this time, and does not replace any of the guidelines. No such new information likely to alter current management of small cell lung cancer has been reported.

I. NEW THERAPEUTIC AGENTS

Gefitinib is an orally active inhibitor of the epidermal growth factor (EGFR) receptor signalling pathway. In two large (210 and 216 patients) randomised Phase II studies in non-small cell lung cancer patients whose disease had progressed after or failed to respond to systemic chemotherapy, gefitinib produced response rates of 18% and 12% and higher rates of reported improvement in patients’ symptoms. Although these were randomised studies, they did not have a control arm receiving supportive care alone or alternative chemotherapy. Two randomised, double-blind Phase III studies totalling over 2,000 patients with mainly stage IV disease comparing first-line chemotherapy with or without gefitinib showed no benefit from its use in this setting. Currently (August 2003) gefitinib is licensed in Australia. Until further comparative studies are available, it should not replace currently approved first or second line chemotherapy. Bronchioloalveolar cell carcinoma appears particularly dependent on EGFR signalling. Gefitinib has shown very promising activity in this subtype, and may become the systemic treatment of choice for this usually resistant condition. A similar drug acting on the same pathway, erlotinib, also has shown activity in non-small cell lung cancer, particularly bronchioloalveolar cell subtype.

Pemetrexed, a novel antifolate drug, has been compared to a currently approved second-line drug, docetaxel, in a Phase III study of 571 patients with advanced non-small cell lung cancer who had received prior chemotherapy. Response rates, time to progression of disease, and survival were not significantly different but pemetrexed resulted in significantly less haematological toxicity and resultant hospitalisations for complications of neutropenia. Pemetrexed thus appears a reasonable alternative to docetaxel as second line chemotherapy, but is not currently approved in Australia for non-small cell lung cancer. No studies evaluating it as part of first-line chemotherapy have been reported yet.
2. FIRST-LINE COMBINATIONS

No new combinations have emerged as superior to those in the guidelines. Meta-analyses have been reported examining the role of platinum versus non-platinum combinations and the optimal number of drugs\(^9,10\). These analyses were based on published trial data and did not consider unpublished trials or individual patient data. The results of these meta-analyses support the use of two drug platinum containing combinations as first-line chemotherapy with single agents, three drug combinations, and non-platinum combinations remaining the subject of further clinical trials. More Phase III trials are now available evaluating the combination of gemcitabine and carboplatin showing better survival that single-agent gemcitabine and older platinum based regimens\(^11,12\). Carboplatin and gemcitabine can now be considered an alternative first line regimen to those in the guidelines. A large Phase III trial has confirmed the role of docetaxel/platinum combinations in first-line chemotherapy\(^13\).

3. CHEMOTHERAPY WITH SURGERY AND/OR RADIATION THERAPY

Longer follow-up has confirmed the benefit of concurrent platinum-based chemotherapy and radiation therapy for good performance status patients with unresected stage III non-small cell lung cancer. The 4-year survival was 21% with concurrent treatment and 12% with sequential treatment with no significant increase in long-term side effects\(^14\). Many Phase II studies have examined different drug combinations with radical irradiation but no new combination has yet been reported in a Phase III study. For good performance status patients with stage IIIA (pN2) disease, a trial of 392 patients compared two different treatment approaches – induction chemotherapy concurrently with moderate-dose radiation followed by surgical resection or concurrent ‘radical’ radiation with chemotherapy and no surgery\(^15\). Initial results did not demonstrate either approach to be clearly superior to the other with better long-term disease control in the surgery arm being counterbalanced by higher treatment related mortality. Currently, either arm of this trial is appropriate until longer term results are available.

The large (355 patient) French study of neoadjuvant chemotherapy has confirmed the benefit of this treatment in operable stage I (not T1N0) – IIIA non-small cell lung cancer showing 5-year survival of 41% with neoadjuvant chemotherapy and surgery and 32% with surgery alone\(^16\). However two recently reported adjuvant chemotherapy trials have been inconsistent. Following surgery for stage I-IIIA disease, 1206 patients were randomised to 3 cycles of platinum-based chemotherapy or observation. No differences in recurrence rate or survival were observed\(^17\). However in another trial of very similar design, 1867 patients received 3–4 cycles of platinum based chemotherapy or observation and the chemotherapy group had statistically significantly improved disease-free and overall survival. In this trial, the 5-year survival rate was 45% with adjuvant chemotherapy and 40% with surgery alone\(^18\). Further trials of adjuvant chemotherapy are expected to report results in the next 12–24 months.
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APPENDIX 5 – ASBESTOS AND OTHER ENVIRONMENTAL CARCINOGENS

Asbestos
Dose-response relationships for asbestos-related lung cancer

Lung cancer and other occupational carcinogens
  Silica and silicosis
  Radiation
    Radon
    Uranium
  Metals
    Arsenic
    Beryllium
    Cadmium
    Chromium
    Haematite
    Nickel
    Tin mining
  Man-made mineral fibres (MMMF)
  Polycyclic aromatic hydrocarbons (PAH) and other environmental pollutants
    PAH
    Diesel exhaust fumes (DEF)
    Cooking oil vapours

Occupations associated with increased risks for lung cancer

Scar cancer of the lung

Diffuse interstitial fibrosis and lung cancer

Pulmonary emphysema and other forms of obstructive airways disease

Adenomatous hyperplasia as a precursor for adenocarcinoma of the lung
There is little doubt that lung cancer related to inhalation of occupational carcinogens is under-recognised across industrialised societies. There are several reasons for this under-recognition: one is that the lung cancer burden across industrialised nations is overwhelmingly attributable to tobacco smoking that physicians may look no further for an explanation for lung cancer among their patients. Although some occupational lung cancers, notably asbestos-related or silica-related lung cancer, may occur in association with other disorders induced by the same occupational factor (for example asbestos-related pleural plaques, asbestosis or silicosis), which may point to the specific carcinogen in some patients (but by no means all), occupational lung cancer per se has no clinical or pathological features that allow its recognition as distinct from the general background of lung cancer in society. It follows that identification of occupational lung cancer is critically dependent upon a systematic and detailed job history.

About 1–5% of the workforce is exposed to carcinogens in the workplace, and about 75% of all occupational cancers affect the lungs and pleura. From the lung cancer to mesothelioma ratio and data from overseas, one can estimate that about 1 000 lung cancers related in part to asbestos exposure occur each year in Australia and about 300 cases related in part to exposure to other lung carcinogens.

Steenland et al estimated that approximately 9 000–10 000 men and 900–1 900 women develop lung cancer each year in the United States because of past exposure to occupational carcinogens, and more than half of these lung cancers are related to asbestos. These authors considered the estimates to be conservative, because (i) the analysis was restricted to confirmed carcinogens only, discounting occupations with excess lung cancer risk but for which the specific carcinogens remained unidentified, and (ii) the estimated numbers of workers exposed was “probably too low”.

In 1992, Teschke and Barroetavena reported that for the years 1980–89, about 0.15% to 0.76% of incident cases of lung cancer were compensated across British Columbia, Saskatchewan and Ontario in Canada. In comparison, the estimated population-attributable risk percentage (PAR%) for lung cancer across the same three provinces was 3–17%. Asbestos was the agent listed for 36% of the lung cancer claims. Teschke and Barroetavena concluded that accepted claims for lung cancer were lower by a factor of four or more than the lowest PAR% estimates from epidemiological studies in the US and Britain, suggesting under-reporting of occupational lung cancer.

**ASBESTOS**

About 4–12% of lung cancers in industrialised societies can be attributed in part to occupational exposure to asbestos. From mesothelioma estimates in Peto et al, one can predict that about 190 000 lung cancer deaths are likely to occur in six nations of Western Europe (Britain, France, Germany, Italy, The Netherlands and Switzerland) over the next 35 years if a lung cancer:mesothelioma ratio of 1:1 holds, and at a ratio of 2:1, the estimate climbs to 380 000. Tossavainen estimates that about 20 000 asbestos-related lung cancers and 10 000 mesotheliomas occur each year across North America, Australia, and seven nations in Western Europe and Scandinavia (combined population ~800 000 000).
The number of officially registered deaths from asbestos-induced diseases in the United Kingdom for the years 1929–96 included 17 999 mesotheliomas (males = 15 298; females = 2 701) and 1 878 lung cancers: a lung cancer to mesothelioma ratio of about 0.1:1. This ratio has shown only minor variation over the years 1988–98 in figures published by the Health & Safety Commission, but an Office of Population Censuses (OPCS) / Health Safety Executive (HSE) document published in 1995 reported that asbestos exposure caused about equal numbers of excess deaths from lung cancer (~200) and mesothelioma (183) for the period 1968–91, a ratio of 1.09:1. In a study of cancer mortality among about 5 100 asbestos factory workers in east London followed for over 30 years since first exposure, the excess lung cancer to mesothelioma ratio was 1.55:1. The analogous ratio in Germany for 1998 was 1.24:1 after introduction in 1992 of the 25 fibres/ml-years’ exposure standard for compensation of asbestos-related lung cancer (747 lung cancers; 602 mesotheliomas).

Lung cancers also appear to be under-represented among asbestos-related diseases compensated in New South Wales (NSW) in Australia. For example, the 1998 Report of the NSW Dust Diseases Board lists the following determinations among 2 338 claims during 1997–98: 96 mesotheliomas in comparison to 9 “asbestos induced carcinomas of the lung”: a lung cancer:mesothelioma ratio of 0.09:1 (for disablement); the certificates for death comprised 104 mesotheliomas versus 14 lung cancers, a ratio of 0.13:1.

Predictions for asbestos-related disorders in Australia (population ~19 000 000) for the years 1987–2020 include about 40 000 cases of lung cancer (range 30 000 to 76 000).

Most asbestos-related lung cancers are attributable to the combined effects of asbestos and tobacco smoke, so that it is necessary to allow for cigarette smoking in comparable reference populations not exposed to asbestos in order to estimate the excess number of asbestos-attributable lung cancers. In this respect, the synergy between tobacco smoke and asbestos has been studied more extensively than the analogous synergy between tobacco smoke and other occupational/environmental carcinogens (eg, radiation). In different studies the interaction between asbestos and tobacco smoke for lung cancer induction varies from more than additive to supra-multiplicative, but the relationship approximates a multiplicative model for insulation workers.

The greater carcinogenicity of the amphiboles for the mesothelium in comparison to chrysotile may not extend so clearly to the induction of lung cancer, although an extensive review published in 2 000 reached the conclusion that the amphiboles are substantially more potent for lung cancer induction than chrysotile (as for mesothelioma).

Occupational lung cancers are neoplasms of long latency. Two studies that calculated the latency time from the time of first asbestos exposure to the diagnosis of the lung cancer reported mean lag-times of about 35 years and 44 years respectively. For workers producing asbestos-containing insulation materials, of whom 77% were employed for <2 years, Nicholson et al observed a significantly elevated relative risk for lung cancer that occurred within 10 years and thereafter remained constant throughout the period of observation.
Lung cancer phenotype has no value in either proving or disproving a relationship to asbestos\textsuperscript{14,20} (or other occupational carcinogens). Roggli and Sanders\textsuperscript{21} found that adenocarcinomas predominated among 234 asbestos-associated lung cancers, for three groups delineated (ie. Asbestosis, plaque only and no plaque/no asbestosis groups), with no significant difference in the distribution of the histological types of cancer between the three groups. (In this respect, adenocarcinoma is now also the most frequent histological type of lung cancer unrelated to asbestos.) There seems to be no significant difference in the proportion of peripheral versus central cancers in subjects exposed to asbestos, in comparison to those who were not\textsuperscript{14}.

A predominance of lower lobe carcinomas among asbestos-exposed workers has been recorded in several studies, with an upper lobe to lower lobe ratio that varied from 1:1.5 to 1:3.5\textsuperscript{14}. Other investigators found no difference in the lobar distribution of lung cancer in such workers: Lee et al\textsuperscript{20} and Roggli and Sanders\textsuperscript{21} found that lung cancers in asbestos-exposed individuals were located most often in the upper lobe, in a ratio of up to 3:1\textsuperscript{21}.

**DOSE-RESPONSE RELATIONSHIPS FOR ASBESTOS-RELATED LUNG CANCER**

In most studies, a direct and linear relationship has been demonstrated between relative risk for lung cancer (RR\textsubscript{LCA}) and cumulative exposure to asbestos, including chrysotile and the amphiboles, expressed as:

\[
RR_{LCA} = 1 + K_L + E
\]

where E is cumulative asbestos exposure, expressed as fibres/ml-years (fibre-years), and \(K_L\) is the industry-specific slope of the relationship expressed as the increase in the excess risk (RR\textsubscript{LCA}−1.0) per one fibre-year of exposure. In this respect, a 1991 consensus paper\textsuperscript{22} reviewed five government-sponsored reports that described 15 cohort studies and accepted that RR\textsubscript{LCA} is proportional to cumulative exposure. The value of \(K_L\) varies across cohorts, from 0.0001–0.002 (0.01–0.2% per fibre-year) in miners and for friction products manufacture, to 0.003–0.09 (0.3–9% per fibre-year) in cohorts of asbestos, asbestos cement, asbestos textile, and insulation workers. Positive estimates for \(K_L\) have been obtained in all studies, but some are based on a small number of cases or deaths, and some authorities have suggested an average value of \(K_L = 0.01\) independent of fibre type — after exclusion of chrysotile miners because of their substantially lower RR\textsubscript{LCA} per unit exposure — corresponding to an increase of 1% in RR\textsubscript{LCA} for each fibre-year of exposure. An extensive review by Hodgson and Darnton\textsuperscript{16} reported similar dose-response values for amphiboles (crocidolite and amosite), but lower values for mixed exposures (with a summary increase in risk of 0.47% per fibre/ml-year of exposure), however, this review was based on 17 cohort studies and did not include data and estimates for case-referent studies.
The linearity of the dose-response relationship between asbestos and lung cancer risk has been questioned\textsuperscript{16} — especially whether linearity is maintained at low exposures — because there are no systematic observational data for exposure levels under 1.0 fibre/ml\textsuperscript{23}. However, there is no clear proof that the relationship is non-linear at low exposures and at present the linear model is employed by most occupational health authorities for risk estimates. Recently, a case-referent study from Sweden\textsuperscript{24,25} found that the relationship between cigarette smoke and asbestos approximated an additive model at low asbestos exposures and that the risk per fibre/ml-year was higher than predicted by linear extrapolation from high dose exposures (14% per fibre/ml-year).

Several reviews published between 1991 and 2000 have supported the cumulative exposure model for lung cancer risk as a consequence of asbestos exposure\textsuperscript{14,16,26,27,28,29,30} with no clearly delineated threshold\textsuperscript{16} and with no requirement for asbestosis or diffuse pleural fibrosis as a pre-requisite for attribution of lung cancer to asbestos\textsuperscript{31}:

Criteria for compensation of asbestos-related lung cancer and approaches to apportionment of the relative contributions of asbestos and cigarette smoke to lung cancer induction are discussed elsewhere\textsuperscript{14,30,31,32,33,34,35,36,37}.

**LUNG CANCER AND OTHER OCCUPATIONAL CARCINOGENS**

Apart from asbestos, those substances/processes designated by the International Agency for Research on Cancer (IARC) as probable or definite human lung carcinogens include the following: acrylonitrile, aluminium production, arsenic and certain arsenical compounds, beryllium and its compounds, bis(chloromethyl) ether and chloromethyl ether, cadmium and its compounds, chromium and its compounds, coal gasification, coke production, diesel exhausts, formaldehyde, glass manufacture, iron and steel founding, mustard gas, nickel, non-arsenical pesticides, radon, silica, soot, sulphuric acid mist, talc containing asbestos fibres, and underground haematite mining\textsuperscript{38,39,40,41,42,43,44}.

Detailed consideration of these agents lies beyond the scope of this document and the interested reader is referred to relevant reviews (eg, see Dubrow and Wegman\textsuperscript{5}, Morabia et al\textsuperscript{45}, Harrington and Levy\textsuperscript{47}, Hayes\textsuperscript{48}, Steenland et al\textsuperscript{2}, and Christiani\textsuperscript{49}).

Analysis of the dose-response relationship for many of these factors is confounded by co-existent other lung carcinogens (eg, tobacco smoke, asbestos, silica/silicosis, or radon\textsuperscript{24,50,51}). The interactive effects between such carcinogens and tobacco smoke are discussed at length in a World Health Organization/International Programme on Chemical Safety (WHO/IPCS) monograph published in 1999\textsuperscript{52}.
SILICA AND SILICOSIS

An increased risk of lung cancer has been reported for patients with silicosis\textsuperscript{53-62}. An estimate of the relative risk for silicotics with average smoking is about 3.4 (~1.7 for those with no history of smoking)\textsuperscript{14}. From an analysis of 15 cohort and case-control studies on silicotics, Steenland et al\textsuperscript{60} derived a summary relative risk of 2.80 (CI = 2.50–3.15); in a further analysis of 16 studies with high exposures to silica and without confounding exposures, these authors found a moderate excess risk of lung cancer (RR = 1.33; CI = 1.21–1.45). De Klerk and Musk\textsuperscript{57} found that an award of compensation for silicosis conferred an immediate and constant relative risk of 1.6 for lung cancer. There has long been debate over whether the increased risk of lung cancer with silica exposure is restricted to those with silicosis or whether the increase in risk is a reflection of high cumulative exposure per se\textsuperscript{14,59}. An industry-funded cohort mortality study on North American industrial sand workers\textsuperscript{63,64,65} found that lung cancer risk was “quite strongly related to cumulative exposure”\textsuperscript{64}, but in the absence of chest radiographs a link between silicosis and lung cancer risk could not be addressed.

RADIATION

RADON

Radon ($^{222}\text{Rn}$) is a gaseous product formed during the decay from uranium ($^{238}\text{U}$) to stable lead\textsuperscript{2}. Radon has a half-life of 3.8 days and decays into short-lived radioactive isotopes of bismuth, polonium and lead, known as radon progeny or radon daughters. The daughters represent metal ions that adhere to particles suspended in the air, and their decay is accompanied by the production of $\alpha$-particles. Exposure to radon progeny is usually measured in working levels (WL) and cumulative exposure is expressed as WL-months (WLM); 1.0 WL is any combination of progeny that releases $1.3 \times 10^5$ MeV; alternatively, exposure to radon can be expressed as picocuries per litre (pCi/L)\textsuperscript{2}. One pCi/L is about equivalent to 0.005 WLM and the standard in the US for radon exposure in mines is 4 WLM/year\textsuperscript{2}.

Occupational exposures to radon can occur during mining for uranium\textsuperscript{66-75} and other metals (see following discussion) and in the processing of ores and radioactive materials. Radon is one likely causative factor for the 10–15% of lung cancers that occur among non-smokers. Radon appears to be of particular significance in geographic regions other than Australia\textsuperscript{74,76,77}, related to well-insulated airtight homes in cold climates, and with basements where the radon gas tends to accumulate\textsuperscript{78} (in the US, radon measuring devices are available in the market place).

The association between radon and lung cancer appears to be well founded\textsuperscript{2,24,79,80,81,82} and epidemiological studies have shown an increased risk of lung cancer with increasing exposures to radon or its decay products. For miners, the excess relative risk for lung cancer is about 1–2% per WLM\textsuperscript{2}. 
There is also evidence of synergy between radon decay products and cigarette smoke. However, the exact risks to the general population from radon daughters have been the subject of some dispute. There is also some evidence of a possible association between Thorotrust (also an $\alpha$-particle emitter) and small-cell carcinoma of lung.

**URANIUM**

Lung cancer has also been recorded among Navajo uranium miners in this group, there appears to be synergy between the uranium mining and cigarette consumption, but the median cigarette consumption was small (about 1–3 cigarettes daily). Lung cancer is also recorded among other cohorts of uranium miners, for example in the former Czechoslovakia and the former East Germany, and in workers involved in uranium processing. The risk factor among uranium miners is also $\alpha$-particle emission from radon daughters. MilliSieverts are now used as the radiation unit for uranium mines, although WLM were used in the past.

**METALS**

**ARSENIC**

Epidemiological studies on copper smelter workers clearly demonstrate that inorganic arsenic is a human lung carcinogen; inorganic arsenic is a constituent of most copper ores, and also lead and zinc ores to a lesser extent, and the workers are potentially exposed to arsenic trioxide released during the smelting process. Copper smelter workers have shown a clear dose-response relationship between the standardized mortality ratio for lung cancer and cumulative arsenic exposure expressed as mg/m$^3$-years. The interactive effect with tobacco smoking appeared to be additive rather than multiplicative.

In an analysis of six studies on arsenic and lung cancer, Steenland et al calculated a combined relative risk for lung cancer of 3.69 (CI = 3.06–4.46), with a clear dose-response effect, but they commented that lung cancer risk is primarily a consequence of past high exposures.

**BERYLLIUM**

Exposure to beryllium occurs mainly in mining and refining, and in the manufacture of ceramics and electronic and aerospace equipment. According to NIOSH estimates, about 40 000 workers were exposed to beryllium in the US during the 1980s, and a high proportion of those so exposed showed evidence of impairment of pulmonary function, presumably as a consequence of berylliosis. (In contrast, berylliosis appears to be virtually unknown in Australia.) From an analysis of the Beryllium Case Registry in the US, Steenland and Ward reported a lung cancer SMR of 2.00 (CI = 1.33–2.89) and in a later study, Ward et al reported a lung cancer SMR of 1.24 (CI = 1.10–1.39), from analysis of 9,225 workers across seven beryllium plants in Ohio and Pennsylvania.
CADMIUM
Cadmium is used mainly for electroplating, as a component of electrodes in batteries, and in alloys. Exposure is usually by inhalation. A study on a US plant where cadmium oxide and sulphide and metal were recovered from wastes from lead and zinc smelters showed a lung cancer relative risk of 1.49 (CI = 0.96–2.22); a dose-response effect was observed and the lung cancer relative risk was significant for workers with the highest exposures (RR = 2.72; CI = 1.24–5.18).

CHROMIUM
There have been more than 50 studies on lung cancer among chromium workers: Steenland et al. estimate the overall relative risk for lung cancer across these studies to be 2.78 (CI = 2.47–3.52) (see also Sorahan). The chromium in most of its compounds is in the trivalent (CrIII) or hexavalent state (CrVI); CrVI induces cancer in experimental animals, but CrIII does not.

HAEMATITE
An excess risk of lung cancer has also been reported among Chinese haematite miners (SMR = 370), but silica, radon and arsenic represent confounding factors for evaluation of the risk among iron ore miners, especially for those who worked underground.

NICKEL
A 1990 IARC report on nickel carcinogenesis found that the rate of lung and nasal cancer was significantly increased among workers at nickel refineries. Steenland et al. estimated the combined relative risk to be 1.56 (CI = 1.41–1.73). Studies of nickel alloy workers and stainless steel welders have not demonstrated a consistently increased number of lung cancer deaths. There is evidence that different nickel compounds confer different risks for lung cancer; although nickel carbonyl is responsible for “almost all” cases of acute nickel toxicity, there are few data to indicate that metallic nickel increases the risk of cancer, and the identity of the compound(s) responsible for the increased risk of lung cancer remains unclear.

TIN MINING
A high incidence of lung cancer has been reported among tin miners in Yunnan, China. Exposures in the mines appear to be complex and to include arsenic, radon progeny and silica. After adjustment for arsenic, age, year of starting work and tobacco smoking, subjects with the highest radon exposure had an odds ratio of 9.5, and risk increased with the duration of exposure. When adjustments were carried out for tobacco use and radon exposure, workers with the highest arsenic exposure had a relative risk of lung cancer of 22.6. In another group in Guangxi province, investigators found a synergistic effect between cigarette smoking and measures of occupational exposure.
MAN-MADE MINERAL FIBRES (MMMF)

An elevated standardised mortality ratio for lung cancer has been reported in cohorts of workers involved in the production of MMMF (including rockwool/slagwool), notably in the early technological phases\textsuperscript{102,103}, when other carcinogens were also present in the workplace (arsenic, asbestos, and polycyclic aromatic hydrocarbons) and quantitative data on tobacco smoking and airborne fibre concentrations were lacking. It is, thus, not possible to ascertain whether the risk of lung cancer was related to the MMMFs themselves. Rödelsperger et al\textsuperscript{104} found that asbestos was a confounding factor for assessment of the carcinogenicity of MMMFs. The carcinogenicity of MMMFs and other fibrous and non-fibrous substitutes for asbestos has been reviewed in detail elsewhere\textsuperscript{15}. The appears to be no convincing evidence that inhaled fibreglass is carcinogenic in humans.

POLYCYCLIC AROMATIC HYDROCARBONS (PAH) AND OTHER ENVIRONMENTAL POLLUTANTS

PAH

PAH are produced mainly by pyrolysis or incomplete combustion of organic substances and they comprise the major sub-group of this family of compounds\textsuperscript{49}. Occupational settings that involve potential exposure to PAH include aluminium production, iron and steel foundry work, coke production and coal gasification. Ash from fuel combustion and diesel exhaust fumes also contains PAH. Accordingly, occupational exposures to PAH are common, and it has been estimated that over two million workers were exposed to PAH worldwide in the mid-1980s\textsuperscript{49}. Epidemiological studies have demonstrated an elevated risk of lung cancer among workers involved in the production of coke, with a relative risk of about 15. Other studies have shown smaller but still elevated risk of lung cancer of about 2.55–3.66\textsuperscript{49}.

DIESEL EXHAUST FUMES

Diesel exhaust is a complex mixture of gas-phase and particulate-phase chemicals that include substances known to be genotoxic or carcinogenic, including polycyclic aromatic hydrocarbons. Multiple studies over the years have returned conflicting data on whether inhaled diesel exhaust fumes (DEF) are carcinogenic in humans\textsuperscript{105–119}, but there appears to be increasing evidence that DEF does increase the risk of lung cancer\textsuperscript{105,108,109,115,117,118,119}. There seems to be an interactive synergy between DEF and cigarette smoke for lung cancer risk: in a study of Swedish dock workers, Emmelin\textsuperscript{109} found an odds ratio of 1.6 (for medium DEF exposure) and 2.9 for high DEF exposures among non-smokers; for the smokers, the respective odds ratios were 10.7 and 28.9. In a meta-analysis of studies on DEF, Lipsett and Campleman\textsuperscript{117} estimated the pooled smoking-adjusted lung cancer risk from DEF to be 1.47. In a detailed case-referent
analysis from Sweden, Gustavsson et al\textsuperscript{24,25} found that for the highest quartile of cumulative exposure to diesel exhaust fumes versus no exposure, the relative risk of lung cancer was 1.63 (CI = 1.14–2.33) and was 1.60 for other combustion products (CI = 1.09–2.34).

**COOKING OIL VAPOURS**

Several studies have reported an increased risk of lung cancer among Chinese women who inhale volatile substances released from heated cooking oils, especially for non-smokers with adenocarcinoma\textsuperscript{120,121,122,123,124}. Fumes from heated cooking oils contain different substances that are genotoxic, mutagenic and carcinogenic, including polycyclic aromatic hydrocarbons such as benzo[a]pyrene and dibenzanthracene\textsuperscript{125–132}. The risk appears to be greatest with use of unrefined rapeseed oil for cooking. Zhong et al\textsuperscript{122} recorded an odds ratio of 1.84 with use of rapeseed oil and an odds ratio of 2.38 according to the smokiness of the oil.

<table>
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<tr>
<td><strong>Occupational carcinogen</strong></td>
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<td>Arsenic</td>
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<td>Beryllium</td>
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<tr>
<td>Cadmium</td>
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<td>Chromium, especially hexavalent chromium</td>
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<tr>
<td>Cooking oils</td>
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<td>Haematite</td>
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<td>Man-made mineral fibres</td>
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<td>Nickel</td>
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OCCUPATIONS ASSOCIATED WITH INCREASED RISKS FOR LUNG CANCER

In 1992, Morabia et al\textsuperscript{133} reviewed multiple case-control studies that evaluated occupational risk factors for lung cancer, and they also carried out a multi-centre case-control study of 24 hospitals in nine metropolitan areas in the United States. They found that the following occupations had a significant increase in the risk of lung cancer independent of cigarette smoking: sheet metal workers and tinsmiths; crane-men, derrick-men, and hoist-men; heated-metal workers; construction labourers and electricians, and bookbinders and related printing trade workers. In all these occupations, the workers were exposed to known or suspected carcinogens that included asbestos, nickel, chromium, PAH and diesel exhaust fumes. Burns and Swanson\textsuperscript{134} analysed incident lung cancer cases by occupation and industry groups and found an elevated risk of lung cancer in the following occupations: excavating and mining workers (OR = 4.01); furnace workers (OR = 3.11); armed services personnel (OR = 3.10); agricultural workers (OR = 2.05); mechanics (restricted to black males: OR = 4.16); painters (OR = 1.96); and drivers (OR = 1.88). Industries with an elevated risk of lung cancer included farming (OR = 2.21), mining (OR = 2.98), and primary ferrous metals manufacture (OR = 2.43). Five of the occupations found more often among lung cancer cases had probable exposure to diesel exhaust fumes. Other occupations with reported increased lung cancer relative risks include shoe manufacture and repairs. For some industries, the excess risk appears to be attributable to asbestos (eg, pulp and paper manufacture).

For asbestos-related neoplasia, the main occupational groups at carcinogenic risk during the 1990s and beyond have been the end-users of asbestos-containing products, including building construction and demolition workers, insulation workers and shipyard workers\textsuperscript{15}.

SCAR CANCER OF LUNG

Although the literature does contain persuasive reports of lung cancers that appeared to develop in pre-existing scars, there is compelling evidence, based on the pattern of collapse and fibrosis in pulmonary scars and collagen fibre analysis, that the scar tissue in most “scar cancers” is secondary to the presence of the carcinoma — a desmoplastic response to the tumour, analogous to the central desmoplasia of breast cancers\textsuperscript{135,136,137,138}.
Lung cancer is well recognised in patients with progressive systemic sclerosis (scleroderma) and other forms of diffuse interstitial fibrosis (DIF) that include usual interstitial pneumonia (UIP; cryptogenic fibrosing alveolitis)\textsuperscript{14}. Turner-Warwick et al\textsuperscript{139} reported the development of lung cancer in 12.9\% of 155 patients with UIP followed to death. The relative risk for lung cancer was 14.1 in comparison to the general population of comparable age and gender, allowing for the length of follow-up for the UIP cohort. The relative risk for male smokers was 14.2 and was 6.7 for female smokers. The proportions of the histological types did not obviously differ from those found in patients without pulmonary fibrosis. (By way of comparison, a report from the same hospital on mortality in 155 cases of asbestosis revealed that lung cancer was present in 44\%.) In a study from Japan, Nagai et al\textsuperscript{140} reported lung cancer in 38\% of patients with DIF who were smokers and in 11\% of the same group who were non-smokers. Nonetheless, in this study 88\% of the tumours were peripheral in distribution and the diagnosis in 27 out of 31 cases was established by transbronchial biopsy of lung (in limited samples of this type, there is a problem in distinguishing between genuine lung cancer and the reactive bronchiolo-alveolar epithelial proliferation that is an almost invariable accompaniment of DIF).

In contrast, Wells and Mannino\textsuperscript{141} found a 5\% rate of association between DIF and lung cancer in the United States in comparison to 27\% for asbestosis and lung cancer, as assessed from death certificates. In this respect, there is an extraordinary association between asbestosis and lung cancer, so that lung cancer occurs in about 25–45\% of cases or more and is now the leading cause of death among asbestotics\textsuperscript{14}. Oksa et al\textsuperscript{142} identified 11 lung cancers in 24 patients with progressive asbestosis (46\%; standardized incidence rate SIR = 37), in comparison to 5/54 non-progressors (9\%; SIR = 4.3).

Mizushima and Kobayashi\textsuperscript{143} reviewed 154 Japanese cases of lung cancer that occurred on a background of idiopathic DIF. These cancers were found predominantly in males (most were smokers). The histological types were the same as lung cancers among patients without interstitial fibrosis, except for a higher proportion of small cell carcinoma. The tumours were mainly peripheral and located in the lower lobes. However, in an autopsy and live case control study of Japanese IPF cases, Iwai et al\textsuperscript{144} found that the IPF rate was twice as high among those whose occupations involved exposure to dusts and organic solvents than workers in other jobs. The live case-control study showed an relative risk of 1.34 for IPF among cadmium, chromium and lead metal production workers in comparison to the non-exposed. Some of the substances implicated in the IPF cases have also been implicated in lung carcinogenesis.
PULMONARY EMPHYSEMA AND OTHER FORMS OF OBSTRUCTIVE AIRWAYS DISEASE

From case-control studies and analysis of lung cancers among lifelong non-smokers and former smokers, elevated lung cancer odds ratios have been found for emphysema, chronic bronchitis and asthma, after adjustment for active and passive smoking\textsuperscript{145,133} (see Table 4–1). The risk was greater for squamous cell carcinoma and for diagnosis of these disorders at older ages. However, as discussed in an earlier section of this document, these findings were non-significant after adjustment for other variables and confounding factors\textsuperscript{145,146}.

ADENOMATOUS HYPERPLASIA AS A PRECURSOR FOR ADENOCARCINOMA OF THE LUNG

Foci of atypical adenomatous hyperplasia in lung tissue have been invoked as a precursor for peripheral adenocarcinoma (see Kerr\textsuperscript{147} for an extensive review and references). These lesions take the form of small poorly circumscribed foci of thickening of alveolar septa with cuboidalisation or proliferation of the lining alveolar epithelial cells that show features of Clara cell or type II pneumocyte differentiation. Nuclear atypia and pleomorphism are usually mild in degree but some lesions display high-grade atypia (about 25–30%). The degree of atypia tends to increase with increasing size of the lesions. Some authorities set an upper size limit of 5 mm for these lesions and classify any similar lesion > 5 mm in diameter as adenocarcinoma. The reported frequency of atypical adenomatous hyperplasia is very variable and depend in part on the diligence with which these lesions are sought and on the presence or absence of other pathological changes in lung tissue (eg, emphysema or pneumonitis). These lesions are probably multiple in most cases, and they are seen most often in lung tissue resected for primary lung cancer (about 9–21.5% of cases) in comparison to lung tissue removed for other reasons (about 4.5–10%). Focal adenomatous hyperplasia is more strongly associated with adenocarcinoma than other histological types of lung cancer. The prevailing evidence indicates that these lesions are involved in a sequence from dysplasia/adenoma to carcinoma, and loss of heterozygosity, p53, c-erb-2 and k-ras mutations are described in these atypical foci.

References


39. IARC. Monographs on the evaluation of carcinogenic risks to humans: chemicals and industrial processes associated with cancers in humans. 1979. Lyon, France, IARC.


44. IARC. Beryllium, cadmium, mercury and exposures in the glass manufacturing industry. Monograph 58. 1993. Lyon, France, IARC.


95. Chromium, nickel and welding. 49. 1990. Lyon, France, IARC.


148. Chromium, nickel and welding. 49. 1990. Lyon, France, IARC.

149. Monographs on the evaluation of carcinogenic risks to humans vol 68. Silica, some silicates, coal dust and para-aramid fibrils. 1997. Lyon, France, IARC.
APPENDIX 6 – NATIONAL TOBACCO STRATEGY
ACTION PLAN

An action plan under the National Drug Strategic Framework, the National Tobacco Strategy 1999 to 2002–03 (NTS) was endorsed by the Ministerial Council on Drug Strategy (MCDS) in June 1999. (see http://www.nationaldrugstrategy.gov.au – under Campaign Sites)

The NTS comprises a range of tobacco control initiatives ultimately designed to improve the health of all Australians by eliminating or reducing their exposure to tobacco in all its forms.

It emphasises a national collaborative approach to tobacco control issues, nominating a range of government, non government and community partnerships and links, under six main key strategy areas:

• strengthening community action
• promoting cessation of tobacco use
• reducing availability and supply of tobacco
• reducing tobacco promotion
• regulating tobacco
• reducing exposure to environmental tobacco smoke.

While the overriding intention of the Strategy is to improve the health of all Australians, the following specific objectives support this goal:

• preventing uptake of tobacco use in non-smokers, especially children and young people
• reducing the number of users of tobacco products
• reducing the exposure of users to the harmful health consequences of tobacco products
• Reducing exposure to tobacco smoke.

Initiatives implemented in the first 18 months of the NTS fall within the following areas:

• national tobacco campaigns
• indigenous tobacco control
• best practice in smoking cessation (see below)
• review of the national quitline
• sales to minors
• health warnings
• tobacco advertising bans
• nicotine regulation
• disclosure of cigarette ingredients
• environmental tobacco smoke.
Several initiatives in the strategy are particularly relevant to Medical Practitioners. One such project is a review of best practice in smoking cessation. The National Heart Foundation was commissioned in September 2000 to identify best practice in brief intervention for smoking cessation in a range of health care settings by professionals such as General Practitioners. This stage was completed in early 2001. The second stage of the project will build on the first to develop and promote the uptake of guidelines in smoking cessation. See also Smoking Cessation in chapter 2.

Importantly, there is also considerable help and services available to smokers wishing to quit from state Cancer Council and QUIT.

APPENDIX 7 – LEVELS OF EVIDENCE FOR DIAGNOSTIC TESTS

I  Evidence obtained from at least one validating cohort study with good reference standards (+/- systematic review) or near 100% sensitivity and specificity of the diagnostic procedure.

II  Evidence obtained from at least one exploratory cohort study with good reference standards (+/- systematic review)

III  Evidence obtained from non-consecutive study or without consistently applied reference standards (+/- systematic review)

IV  Evidence obtained from case-control study or with poor or non-independent reference standard

Reference
APPENDIX 8 – A MODEL FOR PATHOLOGY REPORTING OF LUNG CANCER

NEPEAN HOSPITAL LUNG CANCER REPORTING PROTOCOL

1. Specimen type
   – Pneumonectomy / lobectomy / segmentectomy / wedge resection

2. Topography
   – R lung (RUL / RML / RLL)
   – L lung (LUL / LLL)

3. Tumour location

4. Tumour size
   – maximum diameter

5. Tumour type

6. Histological grade
   – well / moderately / poorly differentiated
   – undifferentiated

7. Vessel invasion
   – absent / present
   – if present – state involvement of artery / vein / lymphatic if possible

8. Perineural invasion
   – absent / present

9. Pleural involvement
   – Pleura free of tumour
   – Tumour abuts the visceral pleura but has not breached it
   – Tumour has invaded through the visceral pleura
   – Tumour has invaded through the parietal pleura

10. Bronchial resection margin
    – free of tumour
    – minimum distance between tumour and bronchial resection margin
    – involved by in situ carcinoma
    – percentage of circumference involved
    – involved by invasive carcinoma
    – mucosal or extramucosal (beyond bronchial cartilage)
11. Vascular resection margin
   - free of tumour
   - tumour thrombus present
   - vessel wall involved by tumour

12. Other resection margins
   - hilar soft tissue / others

13. Chest wall
   - involvement of intercostal muscle / soft tissues / ribs
   - tumour absent / present at inked resection margin

14. In situ carcinoma
   - absent / present

15. Non-neoplastic lung

16. Lymph nodes
   - site or level
   - number of positive or tumour free / number received eg. 3/6 or 0/6
   - focal or extensive or complete involvement by tumour
   - extracapsular spread (measure distance)

*Jenny Ma Wyatt 1998*
EXAMPLE OF REPORT USING NEPEAN HOSPITAL PROTOCOL

1. Specimen type: Lobectomy.
3. Tumour location: Peripheral (subpleural).
4. Tumour size: 6cm in maximum diameter.
5. Tumour type: Squamous cell carcinoma.
6. Histological grade: Moderately differentiated.
9. Bronchial resection margin: Squamous cell carcinoma in situ involves approximately 30% of the circumference.
11. Pleural involvement: The tumour has invaded through the parietal pleura.
12. Other resection margins: Free of tumour.
13. Chest wall: The tumour has invaded into intercostal muscle and soft tissues but not the ribs. The inked resection margin is free of tumour.
15. Non-neoplastic lung: Areas of atelectasis but no evidence of tumour.
16. Lymph nodes: Peribronchial lymph nodes – all show anthracosis and sinus histiocytosis but no evidence of tumour (0/7). Level 3 nodes – one of three nodes shows focal involvement by tumour (1/3). This shows extracapsular spread of distance of 0.5mm.

DIAGNOSIS:

RIGHT LOWER LOBE OF LUNG (LOBECTOMY):

SQUAMOUS CELL CARCINOMA
– SQUAMOUS CELL CARCINOMA IN SITU PRESENT AT BRONCHIAL RESECTION MARGIN
– CHEST WALL RESECTION MARGIN FREE OF TUMOUR
– TUMOUR PRESENT IN 1 OF 3 LEVEL THREE LYMPH NODES
– PERIBRONCHIAL LYMPH NODES FREE OF TUMOUR (0/7)
APPENDIX 9 – MEMBERSHIP OF THE AUSTRALIAN CANCER NETWORK MANAGEMENT OF LUNG CANCER GUIDELINE WORKING PARTY

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Dr Kate Brameld Epidemiologist
Dr Mary Brooksbank Palliative Care Physician
Dr Peter Cole Thoracic Surgeon
Dr Sidney Davis Radiation Oncologist
Dr Kwun Fong Respiratory Physician
Ms Ann Gillett-Dunn Consumer
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The Australian Cancer Network would also like to gratefully acknowledge: Lorraine Ivancic, Rosalie Viney and Philip Haywood of Centre Health Economics Research & Evaluation (CHERE), University of Technology, Sydney for their contribution of Chapter 10 - “Cost effectiveness”, Dr Renee Manser, Clinical Epidemiology and Health Services Evaluation Unit, The Royal Melbourne Hospital, for her contribution on Screening for lung cancer, Dr Jan Copeland, National Drug and Alcohol Centre UNSW, for review of segment on ‘Cannabis and lung cancer’, Dr Jenny Ma Wyatt for permission to incorporate Appendix 8 - “A model for pathology reporting of lung cancer” and to Ms Anna Takacs for assistance with editing.
## APPENDIX 10 – SUBMISSIONS RECEIVED FOLLOWING PUBLIC CONSULTATION

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Clinical practice guidelines for the prevention, diagnosis and management of lung cancer have been prepared by the Australian Cancer Network (ACN) following the outline of National Health and Medical Research Council’s (NHMRC) A guide to the development, implementation and evaluation of clinical practice guidelines (NHMRC Canberra 1999). The ACN Lung Cancer Working Party (see Appendix 9) under the Chairmanship of Associate Professor David Ball has co-ordinated the development of the guidelines.

Lung cancer treatment is a challenge to multiple disciplines. Accordingly the Working Party was representative of Royal Colleges and specialty groups. It comprised representatives from all aspects of clinical practice, including epidemiology, thoracic medicine, thoracic surgery, pathology, medical and radiation oncology, psychosocial medicine, radiology, general practice, nursing, palliative care, medical economics and consumer advocacy.

PURPOSE, SCOPE AND DEVELOPMENT PROCESS OF GUIDELINES

The development of the guidelines was prompted by a number of factors as outlined in the Foreword, where the burden of lung cancer is highlighted and where it is recorded that a somewhat nihilistic attitude towards lung cancer had led to paucity of treatment, with further studies revealing a lack of accord or agreed approach to the management of patients with cancer of the lung.

The prime reason to produce guidelines was to assist in education and improve practice and the quality of care provided by practitioners treating those with lung cancer in Australia. The general practitioner is usually the doctor of first contact, although each individual general practitioner may only see one, or at most, two lung cancer patients a year. It was an important principle to the Working Party that guidelines can improve consistency of care and of patient outcomes1,2.

References


A specially formatted document will be prepared for general practitioners when the current document is accredited. The general practitioner document will provide sound guidance on referral to appropriate specialists. A consumer document will be developed at the same time.

The Working Party was established with the approval and support of The Thoracic Society of Australia and New Zealand, The Australian Lung Foundation and the Royal Colleges. It first met in April 2000 in Melbourne. The aim of the Working Party was to develop guidelines to:

- Assist decision-making in the management of lung cancer
- Provide better understanding through education to all involved in the care of people with lung cancer
- Assess and assure the quality of care
- Improve clinical care
- Bring issues of cost-effectiveness into the public arena.

Clinical practice guidelines provide a framework within which to apply clinical judgement and consider individual patient needs, while providing a milieu for interactive discussion for the patient. In providing such a background, the guidelines are not rigid procedural paths; rather their objective is to ensure that both clinicians and patients are clearly informed about the risks and benefits of the recommended interventions. It is acknowledged that some variations in clinical practice may reflect reasonable differences in clinical judgement, clinical situations and patient preferences and needs.

The guidelines are based on key principles which underpin the NHMRC’s recommendations for guideline development. These are:

- a focus on the improvement of patient outcomes
- a basis in the best available scientific evidence
- inclusion of statements concerning the strength of the recommendations and
- the adoption of a multidisciplinary approach that involves all stakeholders, including consumers.
PROCESS EMPLOYED

The Working Party approached the development of guidelines by setting itself five key tasks.

Task 1. Identification of the known clinical problems and areas of uncertainty in each of the disciplines involved in lung cancer treatment.

Task 2. Collection and review of scientific evidence, including meta-analyses, to identify the best and most appropriate practice for the various interventions in lung cancer treatment.

Task 3. Collaboration of appropriate subgroups, to review and present special issues for the consideration of the full working group.


Task 5. A review and revision process following public consultation as required by NHMRC.

The activity of the Working Party was conducted across Australia, with face-to-face meetings used primarily to identify the scope of the guidelines and to review out-of-session activity. The final editing before submission to NHMRC was conducted by the Chair and an Executive Group from the Working Party.

TASK 1

It was established that the guidelines should focus on recommendations that would improve the outcomes of patients with lung cancer and they would have a strong clinical emphasis.

The Working Party considered it vitally important to distil the best elements of clinical management. To achieve this the Working Party was to consult widely with clinicians and to involve consumers to ensure that the resultant guidelines gained broad acceptance.

TASK 2

Evidence was obtained through various avenues, including PubMed, Medline, CancerLit, Cochrane reviews and personal databases. Identified evidence was then exhaustively evaluated by the Working Party. Analysis of the reviewed literature elicited a number of principles that were incorporated in the guidelines. Each of the papers offered by members of the Working Party to support arguments was evaluated before being incorporated as a reference or rejected if it did not meet the specific criteria applied to the clinical area.
Since decisions may have to be made in the presence of low level published evidence, a number of recommendations are based on level IV evidence. For those recommendations for which level I – IV evidence was lacking, conclusions were drawn from the considered opinion of clinical experts. The processes used in developing these guidelines were designed to ensure that, as far as possible, the recommendations reflect a consensus of those concerned with the treatment of lung cancer in Australia.

The Working Party decided that it was important to give a clear indication in the guidelines as to the strength of the evidence for guidelines and key statements, and to provide references where appropriate.

Relevant data that were not appropriate for developing guidelines were listed as key points.

**DESIGNATION OF LEVELS OF EVIDENCE**

I  Evidence obtained from a systematic review of all relevant randomised controlled trials.

II  Evidence obtained from at least one properly designed randomised controlled trial.

III–1 Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).

III–2 Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.

III–3 Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.

IV  Evidence obtained from case series, either post-test or pre-test and post-test.

(In effect we listed all level III – as III regardless of category.)

These levels of evidence ratings have been adapted from US Preventive Services Task Force (1989), *Guide to clinical preventive services: an assessment of the effectiveness of 169 interventions* (ed M Fisher), Williams and Williams, Baltimore, Appendix A, p388.

TASK 3

During the initial development of these guidelines, the Working Party established clinical assessment subgroups. The leaders of these subgroups identified known clinical problems or issues in their respective fields and consulted more widely, before submitting manuscripts for the whole Working Party’s discussions. This process allowed advancement of the clinical subgroup’s input into the guidelines in the medical oncology, surgery and radiation oncology areas.

Several presentations were made at Annual Meetings (2001, 2002) of The Thoracic Society of Australia and New Zealand, which led to further discussion and refinement of the manuscript. Problem areas were also discussed between Working Party members, their immediate colleagues and more widely in the impromptu clinical networks that strengthen clinical practice in Australia. The result is an agreed document in which the Working Party dealt with and resolved difficult issues.

TASK 4

Members of the Working Party contributed to the compilation of a glossary of lung cancer terms, which forms an appendix to the clinical guidelines. It was based primarily on the ‘Lung cancer guidelines for people with cancer, their families and friends’, published by The Cancer Council Victoria (2000) and is used with their permission.

TASK 5

The guidelines were sent to relevant experts, representatives of professional colleges and consumer representatives. Submissions were also received from others who responded to a public call for submissions by the ACN. Comments received were considered by a special committee chaired by Professor Robert Burton, and decisions to include or exclude comments were based on expert clinical judgement and whether the comments reasonably reflected best practice and the best available evidence. After revision the final drafts for each section were assembled, edited and approved by the Executive Review Group to forward to the NHMRC.

Consumer representation was involved in all stages of guideline development.

TARGET AUDIENCE

The guidelines were developed to equip clinicians with recommendations for the optimal care of people with lung cancer.
COSTING ISSUES

A review of the existing literature on cost-effectiveness of a variety of treatments was undertaken.

IMPLEMENTATION AND DISSEMINATION

The ACN is responsible for disseminating, implementing, evaluating and updating the guidelines. Evaluation and updating processes will be in accordance with NHMRC guidelines. The guidelines will also feature strongly in the accreditation and credentialing activity of the ACN.

The implementation plan includes the following strategies:

APPROVAL

Guideline approval by NHMRC was given and the document will be circulated to relevant stakeholders as a critical first step to aid dissemination and implementation.

DISSEMINATION

The initial print run of 6,000 copies of the guidelines will be disseminated to relevant professional groups. Copies will also be made available to allied health organisations, state and territory health authorities, professional colleges and associations, public policy makers, health economists and professional journals.

To assist electronic dissemination, the NHMRC and ACN have included the guidelines on their websites, enabling internet access. The availability of the guidelines will be advertised through the ACN newsletter, ‘Wongi Yabber’, which is published quarterly throughout the year, and distributed to professional colleges, ACN stakeholders and interest groups, including consumers and has a limited overseas circulation.

Lastly, the guidelines have been promoted at a national seminar and a state seminar on lung cancer management, presentations at relevant professional meetings and conferences and submissions to professional journals.

On 5 April 2003, the National Cancer Control Initiative held a meeting in Adelaide ‘Improving the Management of Lung Cancer’. The draft guidelines provided a substantial role in the discussion that took place.

On 20 June 2003, The Cancer Council New South Wales held a meeting ‘Implementing Multidisciplinary Care in Lung Cancer’. Each attendee received a copy of the draft guidelines. The content featured significantly in presentations and small group activity.
CONSULTATION / FEEDBACK

Since acceptability of the guidelines by relevant stakeholders is a critical first step towards their implementation, consultation is an integral part of the implementation process. This is now an integral part of ACN’s program on credentialing and accreditation.

The guidelines were submitted to the NHMRC, following a public consultation process which was conducted by the ACN.

EVALUATION AND UPDATING

An essential part of the guideline development and implementation process is an evaluation of their effectiveness. An evaluation strategy will be drafted at the implementation stage and will include the collection of data to determine the impact of the guidelines on clinician behaviour and patient health outcomes.

The guidelines reflect the best available knowledge at the time of their publication. However, as new evidence emerges from systematic reviews, they will require regular revision in order to maintain validity. The ACN proposes to investigate the most cost-effective means of undertaking this.
APPENDIX 12 – CONTACTS FOR HELP SERVICES

Importantly, there are considerable help services available to smokers wishing to quit, including state Cancer Councils and QUIT.

NATIONALLY

QUITLINE
Ph: 13 18 48

CANCER HELPLINE
The Cancer Helpline provides general information as well as information on local resources. This service can be accessed from anywhere in Australia for the cost of a local call, connecting to local cancer organisations:
Ph: 13 11 20

STATE AND TERRITORY CANCER ORGANISATIONS AND ASSOCIATED NUMBERS

State and Territory Cancer Councils provide information and educational resources on all types of cancers. Some have lending libraries. Many cancer organisations have also developed their own publications about cancer and treatments. To find out about cancer support groups and other local services, State or Territory cancer organisations and the Cancer Helpline should be contacted.

The Cancer Council ACT
159 Maribyrnong Avenue
Kaleen ACT 2617
Ph: (02) 6262 2222
Fax: (02) 6262 2223
Email: reception@actcancer.org
Website: www.cancer.org.au/act/

The Cancer Council New South Wales
153 Dowling St
Woolloomooloo NSW 2011
Ph: (02) 9334 1900
Fax: (02) 9357 2676
Email: laurenb@nswcc.org.au
Website: www.cancercouncil.com.au
## LIST OF ABBREVIATIONS

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ATBC</td>
<td>Alpha-tocopherol beta carotene</td>
</tr>
<tr>
<td>BSC</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>CHART</td>
<td>Continuous hyperfractionated accelerated radiotherapy</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability adjusted life year</td>
</tr>
<tr>
<td>DIF</td>
<td>Diffuse interstitial fibrosis</td>
</tr>
<tr>
<td>ED</td>
<td>Extensive disease</td>
</tr>
<tr>
<td>ELCAP</td>
<td>Early lung cancer action project</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Fluoro-deoxy glucose PET</td>
</tr>
<tr>
<td>FNA</td>
<td>Fine needle aspiration</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Granulocyte colony stimulating factor</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Granulocyte-macrophage colony stimulating factor</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>LD</td>
<td>Limited disease</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>LYS</td>
<td>Life-year saved</td>
</tr>
<tr>
<td>M</td>
<td>Metastases</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>N</td>
<td>Regional lymph nodes</td>
</tr>
<tr>
<td>NCCI</td>
<td>National Cancer Control Initiative</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NRT</td>
<td>Nicotine replacement therapy</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
</tr>
<tr>
<td>OCA</td>
<td>Vincristine, adriamycin and cyclophosphamide</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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</tr>
<tr>
<td>PCI</td>
<td>Prophylactic cranial irradiation</td>
</tr>
<tr>
<td>PE</td>
<td>Cisplatin with etoposide</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PI</td>
<td>Cisplatin with irinotecan</td>
</tr>
<tr>
<td>POHEM</td>
<td>Population health model</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>RRLCA</td>
<td>Relative risk for lung cancer</td>
</tr>
<tr>
<td>RTC</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>SCLC</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardised mortality rates</td>
</tr>
<tr>
<td>SPN</td>
<td>Solitary pulmonary nodule</td>
</tr>
<tr>
<td>SVCO</td>
<td>Superior vena cava obstruction</td>
</tr>
<tr>
<td>T</td>
<td>Primary tumour</td>
</tr>
<tr>
<td>TRT</td>
<td>Thoracic radiotherapy</td>
</tr>
<tr>
<td>UICC</td>
<td>International Union Against Cancer</td>
</tr>
<tr>
<td>VATS</td>
<td>Video-assisted thoracoscopic techniques</td>
</tr>
<tr>
<td>YLD</td>
<td>Years lost due to disability</td>
</tr>
<tr>
<td>YLL</td>
<td>Years of life lost</td>
</tr>
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## Glossary

<table>
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<th>Definition</th>
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<tr>
<td>abdomen</td>
<td>The part of the body between the chest and hips, which contains the stomach, liver, intestines, bladder and kidneys.</td>
</tr>
<tr>
<td>adenocarcinoma</td>
<td>A type of lung cancer that starts in the bronchial glands that are found in the mucous membrane lining the airways.</td>
</tr>
<tr>
<td>adjuvant chemotherapy</td>
<td>Chemotherapy that is used in a supplementary but not chemotherapy dominant therapy.</td>
</tr>
<tr>
<td>advanced cancer</td>
<td>Cancer that has metastasised and/or is unlikely to be cured.</td>
</tr>
<tr>
<td>alveoli</td>
<td>The tiny air sacs in the lungs; an adult has about 300 million. When air is breathed in, it goes via the airways to the alveoli, where oxygen is taken from them into the bloodstream.</td>
</tr>
<tr>
<td>anaesthetic</td>
<td>A drug that is taken to stop a person feeling pain during a medical procedure. A local anaesthetic numbs only a part of the body; a general anaesthetic causes a person to lose consciousness for a period of time.</td>
</tr>
<tr>
<td>asbestosis</td>
<td>A slowly progressing lung disease caused by asbestos. It is not a cancer.</td>
</tr>
<tr>
<td>benign</td>
<td>Not cancerous. Benign cells are not able to spread like cancer cells.</td>
</tr>
<tr>
<td>biopsy</td>
<td>The removal of a small sample of tissue from the body, for examination under a microscope, to help diagnose a disease.</td>
</tr>
<tr>
<td>brachytherapy</td>
<td>A type of radiotherapy applicable to tumours which involves insertion of radioactive seeds directly into the tumour, which are retained (low dose brachytherapy). Another form is high dose brachytherapy, which involves treatment by temporary insertion of radioactive catheters into the tumour.</td>
</tr>
<tr>
<td>bronchi/bronchioles</td>
<td>Bronchi are the larger tubes that carry air in the lungs. Bronchioles are the tiny tubes that carry air to the outer parts of the lungs.</td>
</tr>
<tr>
<td>bronchoscopy</td>
<td>An examination in which a tube is passed through the nose or the mouth into the lungs so that they can be examined for disease and some tissue sampled, if necessary.</td>
</tr>
<tr>
<td>carcinoma</td>
<td>A cancer that arises in the tissue that lines the skin and internal organs of the body.</td>
</tr>
<tr>
<td>cells</td>
<td>The ‘building blocks’ of the body. A human is made of millions of cells, which are adapted for different functions. Cells are able to reproduce themselves exactly, unless they are abnormal or damaged, as are cancer cells.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>chemotherapy</td>
<td>The use of special (cytotoxic) drugs to treat cancer by killing cancer cells or slowing their growth.</td>
</tr>
<tr>
<td>chest cavity</td>
<td>The area enclosed by the ribs, above the diaphragm.</td>
</tr>
<tr>
<td>CT scanning</td>
<td>Computerised tomography is a technique for constructing pictures from cross sections of the body, by x-raying from many different angles the part of the body to be examined.</td>
</tr>
<tr>
<td>diaphragm</td>
<td>A dome-like sheet of muscle that divides the chest cavity from the abdomen. It is used in breathing.</td>
</tr>
<tr>
<td>emphysema</td>
<td>A condition in which the alveoli of the lungs are enlarged and damaged, which reduces the lung's surface area, causing breathing difficulties.</td>
</tr>
<tr>
<td>FNA</td>
<td>Fine needle aspiration is a procedure in which a fine needle is used to suck up a few cells from a tumour, for biopsy.</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluoro-deoxy glucose (see PET scanning)</td>
</tr>
<tr>
<td>hamartoma</td>
<td>A benign local malformation resembling a neoplasm resulting from faulty development in an organ - frequently marked by one cell type.</td>
</tr>
<tr>
<td>helical (spiral) CT scanning</td>
<td>Patient moves continuously through a scanner without any stopping. The path of the beam through the patient is a continuous helix.</td>
</tr>
<tr>
<td>large cell carcinoma</td>
<td>A type of lung cancer that usually develops in the airways and is characterised by large rounded cells.</td>
</tr>
<tr>
<td>lobectomy</td>
<td>A surgical operation to remove a lobe of a lung.</td>
</tr>
<tr>
<td>lobes</td>
<td>The sections that make up the lungs—the left lung has two lobes and the right lung, three.</td>
</tr>
<tr>
<td>lymphatic system</td>
<td>The lymphatic system is part of the immune system, which protects the body against 'invaders', like bacteria and parasites. The lymphatic system is a network of small lymph nodes connected by very thin lymph vessels, which branch into every part of the body.</td>
</tr>
<tr>
<td>lymph nodes</td>
<td>Also called lymph glands. Small, bean-shaped structures which form part of the lymphatic system. Lymph is the fluid that flows through this system and carries cells that help to fight disease and infection. The lymph nodes filter the lymph to remove bacteria and other harmful agents, such as cancer cells.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>MRI</td>
<td>A special imaging technique used to image internal structures of the body. It uses the influence of a large magnet to polarize hydrogen atoms in the tissues and then monitors the summation of the spinning energies within living cells. Images are very clear and are particularly good for soft tissue, brain and spinal cord, joints and abdomen. These scans may be used for detecting some cancers or for following their progress.</td>
</tr>
<tr>
<td>malignant</td>
<td>Cancerous. Malignant cells can spread (metastasise) and can eventually cause death if they cannot be treated.</td>
</tr>
<tr>
<td>mediastinum</td>
<td>The area in the chest cavity between the lungs. It contains the heart and large blood vessels, the oesophagus, the trachea and many lymph nodes.</td>
</tr>
<tr>
<td>mesothelioma</td>
<td>A rare cancer of the membranes around the lungs. Exposure to asbestos can cause mesothelioma.</td>
</tr>
<tr>
<td>metastases</td>
<td>Also known as ‘secondaries’. Tumours or masses of cells that develop when cancer cells break away from the original (primary) cancer and are carried by the lymphatic and blood systems to other parts of the body.</td>
</tr>
<tr>
<td>neo-adjuvant</td>
<td>Chemotherapy that is administered before the dominant therapy, for example, radiotherapy/surgery.</td>
</tr>
<tr>
<td>non-small cell lung carcinoma</td>
<td>One of the two main groups of lung cancers. This group includes squamous cell carcinoma, adenocarcinoma, large cell carcinoma, bronchiolo-alveolar cell carcinoma and mesothelioma.</td>
</tr>
<tr>
<td>odds ratio</td>
<td>The ratio of a part to the remainder. It is used to express the chance that a particular outcome will occur.</td>
</tr>
<tr>
<td>oesophagus</td>
<td>The tube that carries food from the throat to the stomach.</td>
</tr>
<tr>
<td>palliative treatment</td>
<td>Treatment aimed at providing relief for symptoms without attempting to cure the disease.</td>
</tr>
<tr>
<td>peritoneum</td>
<td>The lining of the abdomen.</td>
</tr>
<tr>
<td>PET scan</td>
<td>Positron emission tomography. A technique that is used to build up clear and detailed cross-section pictures of the body. The person is injected with a glucose solution containing a small amount of radioactive material. The PET scanner can ‘see’ the radioactive substance. Damaged or cancerous cells show up as areas where the glucose solution is being used.</td>
</tr>
<tr>
<td>pleura</td>
<td>Membranes that line the chest wall and cover the lungs.</td>
</tr>
<tr>
<td>pleural cavity</td>
<td>A space, normally empty, that lies between the two layers of the pleura.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td>pleural effusion</td>
<td>An abnormal accumulation of fluid in the pleural space. It may be asymptomatic or associated with chest pain, fever and coughing.</td>
</tr>
<tr>
<td>pneumonectomy</td>
<td>A surgical operation to remove a whole lung.</td>
</tr>
<tr>
<td>primary cancer</td>
<td>The original cancer. At some stage, cells from the primary cancer may break away and be carried to other parts of the body, where secondary cancers may form.</td>
</tr>
<tr>
<td>prognosis</td>
<td>An assessment of the course and likely outcome of a person’s disease.</td>
</tr>
<tr>
<td>radiotherapy</td>
<td>The use of radiation, usually x-rays or gamma rays, to kill cancer cells or injure them so they cannot grow and multiply. Radiotherapy treatment can also harm normal cells, but they are able to repair themselves.</td>
</tr>
<tr>
<td>randomised controlled trial (RCT)</td>
<td>A study or experiment where subjects are allocated at random to receive or not receive the treatment, procedure or intervention. The results for each group are compared. Generally held to be the most scientifically rigorous method of testing an hypothesis.</td>
</tr>
<tr>
<td>rapid smoking</td>
<td>Asking subjects to smoke at an increased rate (from the Cochrane database). The version of rapid smoking evaluated in most trials consists of asking subjects to take a puff every 6 or 10 seconds. They smoke for three minutes or until they either consume three cigarettes or feel unable to continue. After a period of rest this procedure is repeated two or three times.</td>
</tr>
<tr>
<td>recurrent cancer</td>
<td>A cancer that grows from cells of a primary cancer that evaded treatment. Recurrent cancer may appear up to 20 years after the primary cancer was treated, depending on the type of cancer.</td>
</tr>
<tr>
<td>relative risk</td>
<td>The risk (of a disease or death) among those exposed to the risk compared to those who are not exposed to the risk.</td>
</tr>
<tr>
<td>relative survival</td>
<td>Relative survival analysis aims to quantify how long someone with a specific disease might survive when compared to the “general population”. The general population are matched to the “disease” cases by age, sex and year of diagnosis. Relative survival is thus the ratio of the proportion of survivors in the disease group to the proportion of survivors in a similar group of people without the disease. A relative survival of 100% would indicate that persons with disease do not die any more rapidly as they age than people without the disease whereas a result of less than 100% indicates that the disease is resulting in premature death, even when other causes of death have been accounted for.</td>
</tr>
<tr>
<td>resection</td>
<td>Surgical removal of a portion of any part of the body.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>small cell carcinoma</td>
<td>A type of lung cancer that is strongly associated with cigarette smoking. It spreads early and causes few initial symptoms.</td>
</tr>
<tr>
<td>sputum</td>
<td>Liquid coughed up from the lungs. Also known as phlegm.</td>
</tr>
<tr>
<td>sputum cytology test</td>
<td>Examination of sputum under a microscope to look for cancer cells.</td>
</tr>
<tr>
<td>squamous cell carcinoma</td>
<td>A cancer found most commonly on skin, but also in inner linings of the body, for example, a lung. It forms in the squamous (scaly) epithelium.</td>
</tr>
<tr>
<td>staging</td>
<td>Investigations to find out how far a cancer has progressed. This is important in planning the best treatment.</td>
</tr>
<tr>
<td>stent</td>
<td>A tube made of metal or plastic that is inserted into a vessel or passage to keep it open and prevent closure when it is under pressure.</td>
</tr>
<tr>
<td>thoracocentesis</td>
<td>A medical procedure to draw fluid or air from the chest, using a hollow needle.</td>
</tr>
<tr>
<td>tissue</td>
<td>A collection of cells.</td>
</tr>
<tr>
<td>tissue biopsy</td>
<td>Examination of tissue, which has been removed from the body, under a microscope so that any abnormalities in the cells can be seen.</td>
</tr>
<tr>
<td>trachea (windpipe)</td>
<td>The pipe through which air passes to reach the lungs. The trachea starts in the neck, immediately below the voice box (larynx), and descends a few centimetres into the chest before branching to form the two bronchi, one of which goes into each lung.</td>
</tr>
<tr>
<td>tumour</td>
<td>A new or abnormal growth of tissue on or in the body.</td>
</tr>
<tr>
<td>wedge resection</td>
<td>A surgical operation to remove a part of a lung, but not a complete lobe.</td>
</tr>
</tbody>
</table>

This glossary was adapted from *Lung Cancer: a guide for people with cancer, their families and friends, Anti-Cancer Council of Victoria, May 2000* with kind permission from The Cancer Council Victoria.
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Note: Locator numbers in italic indicate a table or a figure. Guidelines are highlighted in bold for the convenience of users

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