

## Clinical practice guidelines for the treatment of lung cancer

**This PDF has been made available for reference only.**

Please note that these guidelines have been developed as electronic guidelines and published at:  
[https://wiki.cancer.org.au/australia/Guidelines:Lung\\_cancer](https://wiki.cancer.org.au/australia/Guidelines:Lung_cancer)

We are aware that the formatting in this PDF is not perfect. It has been produced for offline review purposes only

Guidelines commissioned by

**Guidelines commissioned by**

## 1 Clinical practice guidelines for the treatment of lung cancer

---

### 1.1 **Contents**

#### 1.1.1 **Foreword**

#### 1.1.2 **Summary of recommendations**

### 1.2 **Non small-cell lung cancer**

#### 1.2.1 **Stage I operable**

#### 1.2.2 **Surgery**

- Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage I NSCLC?
- Is minimally invasive lobectomy as effective as open lobectomy for treatment of operable stage I NSCLC?

#### 1.2.3 **Radiotherapy**

- What is the role of radiotherapy in the treatment of operable stage I NSCLC?
- What is the role of radiotherapy after surgery in the treatment of operable stage I NSCLC?

#### 1.2.4 **Chemotherapy**

- What is the role of chemotherapy before surgery in the treatment of operable stage I NSCLC?
- What is the role of chemotherapy after surgery in the treatment of operable stage I NSCLC?

### **1.2.5 Stage I inoperable**

#### **1.2.6 Radiotherapy**

- What is the best practice radiotherapy approach in patients with stage I inoperable NSCLC?

#### **1.2.7 Surgery**

- What is the role of radiofrequency ablation in stage I inoperable NSCLC?

#### **1.2.8 Chemotherapy**

- What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage I NSCLC?

### **1.2.9 Stage II operable**

#### **1.2.10 Surgery**

- Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage II NSCLC?

#### **1.2.11 Radiotherapy**

- What is the role of radiotherapy after surgery in the treatment of operable stage II NSCLC?

#### **1.2.12 Chemotherapy**

- What is the role of chemotherapy before surgery in the treatment of operable stage II NSCLC?
- What is the role of chemotherapy after surgery in the treatment of operable stage II NSCLC?

### **1.2.13 Stage II inoperable**

#### **1.2.14 Radiotherapy**

- What is the best practice radiotherapy approach in patients with stage II inoperable NSCLC?

### **1.2.15 Chemotherapy**

- What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage II NSCLC?

### **1.2.16 Stage III operable**

#### **1.2.17 Radiotherapy**

- What is the role of postoperative radiotherapy (PORT) in resected stage III NSCLC?

#### **1.2.18 Surgery**

- What is the clinical benefit of mediastinal lymph node dissection in stage IIIA operable NSCLC?
- What is the clinical benefit of the addition of surgery to definitive chemoradiotherapy in stage IIIA (N2) NSCLC?

#### **1.2.19 Chemotherapy**

- What is the clinical benefit of adjuvant chemotherapy for patients with stage III operable NSCLC?
- What is the clinical benefit of neoadjuvant chemotherapy for patients with stage III operable NSCLC?
- What is the clinical benefit of the addition of neoadjuvant radiotherapy to neoadjuvant chemotherapy in stage IIIA (N2) NSCLC?

### **1.2.20 Stage III inoperable**

#### **1.2.21 Radiotherapy**

- What is the recommended treatment approach for the definitive management of patients with good performance status and inoperable stage III disease?
- What is the optimal radiation dose and fractionation schedule for good performance status patients with inoperable stage III NSCLC undergoing curative therapy?
- What are the principles of radiation therapy in the definitive management of stage III inoperable NSCLC?
- What is the optimal treatment approach for patients with stage III inoperable NSCLC who, because of patient or tumour factors, are not suitable for curative treatment with concurrent chemo-radiotherapy?
- What is the role of prophylactic cranial irradiation (PCI) in patients with stage III NSCLC?
- What is the optimal management of Pancoast tumours?

### **1.2.22 Stage IV operable**

#### **1.2.23 Radiotherapy**

- What is the clinical benefit of adjuvant whole brain radiotherapy following resection or stereotactic radiosurgery to the brain metastasis(es)?

#### **1.2.24 Surgery**

- What is the clinical benefit of video assisted thoracoscopic surgery (VATS) pleurodesis in malignant effusions?
- What is the clinical benefit of resection of brain metastasis?
- What is the clinical benefit of resection of primary disease after complete resection of metastatic disease?

### **1.2.25 Stage IV inoperable**

#### **1.2.26 Radiotherapy**

- What is the clinical benefit of radiotherapy to the lung primary in stage IV NSCLC?
- What is the clinical benefit of radiotherapy to the brain for patients with inoperable brain metastases from NSCLC?
- What is the role of stereotactic radiosurgery in the treatment of brain metastases?
- What is the clinical benefit of radiotherapy to the bone for metastatic disease from NSCLC?
- What is the clinical benefit of radiotherapy in metastatic spinal cord compression?

#### **1.2.27 Chemotherapy**

- What is the optimal systemic therapy for stage IV inoperable NSCLC?

## **1.3 Small cell lung cancer**

### **Limited stage**

#### **1.3.1 Chemotherapy**

- What is the optimal systemic therapy and duration to be used for the treatment of limited stage small cell lung cancer?
- What is the optimal concurrent chemotherapy to be used for the treatment of limited stage small cell lung cancer with radiotherapy?

### **1.3.2 Radiotherapy**

- Which patients with SCLC benefit from prophylactic cranial irradiation?
- What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with limited stage SCLC?
- What is the optimal timing of thoracic radiotherapy in patients receiving chemotherapy for limited stage SCLC?
- What is the optimal dose and fractionation schedule of thoracic radiotherapy in patients with limited stage SCLC?
- What is the optimal treatment volume in patients with limited stage SCLC receiving thoracic radiotherapy?

#### **Extensive stage**

### **1.3.3 Chemotherapy**

- What is the optimal chemotherapy regimen and duration of therapy in extensive stage small cell lung cancer in the first-line setting?
- What is the optimal second-line therapy in patients with extensive stage small cell lung cancer?

### **1.3.4 Radiotherapy**

- What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with extensive stage SCLC?
- Is there a role for thoracic radiotherapy in patients with extensive stage SCLC?

## **1.4 Palliative care**

- What is the role of palliative care in symptom management for patients with lung cancer?
- What is the role of advance care planning and timing of referral for patients with lung cancer?
- What is the role of psychological support and interventions in the treatment of lung cancer?

## **1.5 Supportive care**

- What is the role of case management in the treatment of patients with lung cancer?
- What is the role of topical creams, skin moisturisers and maintenance antibiotics in the treatment of rash from anti-EGFR therapy in patients with lung cancer?
- What is the role of early ICC/pleurodesis or early thoracoscopic pleurodesis in the treatment of pleural effusions in patients with stage IV inoperable NSCLC?

## 1.6 Appendices

- Guideline development process
- Working party members and contributors
- Conflict of interest register
- Abbreviations

## 1.7 General comments

Please provide general comments regarding this draft guideline by using the comment button below.

## 1.8 Feedback

# 1 Foreword

---

Guidelines commissioned by

## 1.1 Foreword

---

The first Australian evidence-based “Clinical guidelines for the prevention, diagnosis and management of lung cancer” were published in a paperback format in 2004 with endorsement by the National Health and Medical Research Council. Since then, the lung cancer evidence base has grown almost exponentially, particularly in the area of treatment. By 2010, a revision was long overdue and it was recognised that the printed format was unsuited to keeping pace with the regular stream of new knowledge. The solution proposed by Cancer Council Australia (CCA) was a web accessible electronic version of the guidelines in a “wiki” format that would allow editing and updating by expert standing committees as soon as new evidence became available.

In a project commissioned by Cancer Australia (CA), CCA undertook to develop a sustainable web-based wiki platform with revised guidelines for the treatment of lung cancer as the first topic.

The scope of the revision was limited in this first phase to the treatment of non-small cell and small cell lung cancer (chapters 5 and 6 respectively of the 2004 version) and supporting the patient and palliative care (chapters 4, 7 and 8). A working party of 22 clinicians (see Appendix), representing the range of specialties engaged in treating lung cancer including respiratory medicine, thoracic surgery, radiation oncology, medical

oncology and palliative care, were brought together and assigned topics in their area of expertise. Most Australian states were represented on the working party, and New Zealand was represented in the process by Dr Jeff Garrett. Unlike the 2004 guidelines, in which the content was set out according to treatment modality, we decided to organise the questions according to disease stage. This was an acknowledgment that it is stage rather than modality that is relevant for clinical decision making, and that in each stage, optimal treatment is often multimodality. The questions on palliative care were prepared separately, as it is accepted that referral to palliative care can be appropriate at any stage of the disease.

The importance of the multidisciplinary team in initial assessment, diagnosis and making recommendations about treatment is strongly endorsed for all patients with lung cancer, but the evidence surrounding their role in overall lung cancer management was not within the scope of the current project, and will be addressed in the next phase of the revision.

The working party were asked to prepare questions relevant to their sections, resulting in 54 clinical questions. The project officers conducted a literature search based on those questions, retrieving 22,211 results. After excluding studies with methodologic problems, and further searching, 2,324 articles were identified and forwarded to the authors for appraisal using an online scoring tool derived from the NHMRC principles for assessing clinical evidence.<sup>[1]</sup> Finally, 1,222 articles were deemed worthy of appraisal using the PICO (population, intervention, comparator, outcome) methodology. The authors then wrote brief descriptions of the evidence and summarised it with a grade of recommendation (levels A-C).<sup>[2]</sup> Where the quality of the evidence was below grade C, or it is unlikely there will ever be high level evidence, for example for an uncommon clinical scenario, the authors added practice points. In January 2012, the working party was instructed to review the content using an online commenting tool. One hundred and fifty six (156) working party member comments were received in nine weeks, which fine-tuned the content. The project officer then double checked the grade of recommendation against the source documents.

The draft guidelines containing 127 recommendations and 56 practice points were released online for public consultation for a 30 day period on 1 May 2012. The consultation process involved soliciting public comments by sending email alerts to 256 email recipients comprising relevant professional organisations, state and territory Cancer Councils and individual clinical experts and consumer organisations in Australia and New Zealand, and inviting them to post their comments on the Cancer Council Australia Cancer Guidelines Wiki. During the consultation process, there were 995 visitors to the website. Nineteen (19) submissions were received with 38 comments. These led to further edits to the draft guidelines after the working party considered all the public comments.

The guidelines resulting from this exhaustive and rigorous process are now available online, but they are not final, and never will be. The guidelines represent a living document an interactive forum for comment and debate and an opportunity to bring new evidence to the lung cancer community within a short time frame. We invite readers who become aware of new evidence to create a personal account on the wiki and make comment online in the appropriate section, so that the working party can consider whether it should change any of the recommendations.

Users need to be warned that most of the evidence evaluated necessarily predates the 2010 implementation of the 7th edition of the TNM staging system, and where there are differences between the 6th and 7th editions, this needs to be taken into account when applying the recommendations. There have also been recent changes in the pathology subclassification of adenocarcinoma, and in the molecular characterisation of non-small cell lung cancer, for which the evidence for optimal treatment is still emerging.



Further work on the guidelines will continue, with the topics of prevention, screening, diagnosis and assessment to be considered next.

I believe the wiki guidelines format resulting from this project is internationally unique, and provides a model for others to follow. We hope the wiki will be an accessible up-to-date resource for multi-disciplinary teams, individual clinicians, students and consumers. I congratulate CCA on the wiki's attractive, easy-to-navigate and interactive website, and the features that enable visitors to link to the source literature underpinning the recommendations.

I would like to thank my many colleagues on the working party who gave voluntarily of their time to appraise the evidence, write the recommendations and meet the deadlines. I also thank Cancer Australia's Lung Cancer team and the CEO of Cancer Council Australia, Professor Ian Olver for their support and guidance. And finally I wish to acknowledge the enormous amount of work done by the project team at CCA: Laura Holliday and Alice Winter-Irving, the project officers who sifted the evidence; and Christine Vuletich and Jutta von Dincklage who kept the project moving and provided the professional finish to the product that follows.

**Professor David Ball MB BS, MD, FRANZCR**

**Chair, Lung Cancer Guidelines Working Party**

**Peter MacCallum Cancer Centre, Victoria**

## 1.2 References

---

<references>

1. ↑ National Health and Medical Research Council. *How to use the evidence: assessment and application of scientific evidence*. Commonwealth of Australia: National Health and Medical Research Council; 2000 Jan 1 Available from: [http://www.nhmrc.gov.au/\\_files\\_nhmrc/publications/attachments/cp69.pdf](http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp69.pdf).
2. ↑ National Health and Medical Research Council. *NHMRC levels of evidence and grades for recommendations for guideline developers*. Canberra: National Health and Medical Research Council; 2009 Available from: [https://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/developers/nhmrc\\_levels\\_grades\\_evidence\\_120423.pdf](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf).

## 2 Summary of recommendations

---

Guidelines commissioned by

### 2.1 Summary of recommendations

---

For explanation of levels of evidence and grades for recommendations, see Levels of evidence and grades for recommendations below. You may also like to refer to the Appendix - Guideline development process

## 2.2 Non-small cell lung cancer

Stage I operable

Surgery

### 2.2.1 Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage I NSCLC?

Recommendation	Grade
<p>Systematic lymph node sampling is recommended to rule out occult nodal disease in clinical stage I patients. There is no apparent additional survival benefit of complete mediastinal node dissection in this group of patients.</p> <p>Last reviewed November 2015</p>	<p><b>C</b></p>

#### Point(s)

For accurate staging according to AJCC TNM Pathological Staging, it is advisable to sample at least three lymph nodes from different stations. This is also required for prognostic purposes and for appropriate referral for adjuvant chemotherapy.

Last reviewed November 2015

### 2.2.2 Is minimally invasive lobectomy as effective as open lobectomy for treatment of operable stage I NSCLC?

Recommendation	Grade
<p>Minimally invasive lobectomy is at least as effective as open lobectomy with respect to long term survival and reported post-operative complication rates.</p> <p>Last reviewed December 2015</p>	<p><b>B</b></p>

Radiotherapy

### 2.2.3 What is the role of radiotherapy in the treatment of operable stage I NSCLC?

Recommendation	Grade
<p>In patients with operable stage I NSCLC, surgery is recommended over conventional radiotherapy, but SABR may be a reasonable option for patients refusing an operation, or who are high risk for a lobectomy.</p> <p>Last reviewed December 2015</p>	<p><b>D</b></p>

Point(s)
<p>Radiotherapy is an alternative treatment option for patients with stage I NSCLC who refuse surgery or are not fit for a standard lobectomy. There is insufficient evidence to recommend which method of radiotherapy (conventional or SABR) is preferable. In patients with peripherally situated tumours five cm or less in diameter, SABR is a reasonable treatment option. For larger tumours or those in less favourable anatomical sites near organs at risk, it may be reasonable, for patient convenience, to moderately accelerate treatment e.g. 50-55Gy in 20 fractions (extrapolating from Price et al 2012).</p> <p>Last reviewed December 2015</p>

### 2.2.4 What is the role of radiotherapy after surgery in the treatment of operable stage I NSCLC?

Recommendation	Grade
<p>In patients who have had complete resection of stage I NSCLC, postoperative radiotherapy is not recommended.</p> <p>Last reviewed December 2015</p>	<p><b>A</b></p>
<p>I-125 seed brachytherapy to the tumour bed is not recommended after sublobar resection for stage I NSCLC.</p> <p>Last reviewed December 2015</p>	<p><b>B</b></p>

**Point(s)**

In the absence of any evidence regarding the treatment of incompletely resected stage I disease (positive margins) unsuitable for further surgery, expert consensus opinion recommends that radiotherapy be given to the site of residual disease using the same dose and technique as if no resection had been performed.

Last reviewed December 2015

Chemotherapy

**2.2.5 What is the role of chemotherapy before surgery in the treatment of operable stage I NSCLC?**

<b>Recommendation</b>	<b>Grade</b>
Neoadjuvant chemotherapy is not considered standard therapy for stage IA NSCLC. Last reviewed December 2015	<b>B</b>
Neoadjuvant chemotherapy is not considered standard therapy for stage IB NSCLC. Last reviewed December 2015	<b>B</b>

**2.2.6 What is the role of chemotherapy after surgery in the treatment of operable stage I NSCLC?**

<b>Recommendation</b>	<b>Grade</b>
Post-operative adjuvant chemotherapy is not recommended for stage IA NSCLC. Last reviewed December 2015	<b>B</b>
Platinum-based adjuvant chemotherapy is recommended for all patients with stage IB NSCLC. Last reviewed December 2015	<b>B</b>

Stage I inoperable  
Radiotherapy

## 2.2.7 What is the best practice radiotherapy approach in patients with stage I inoperable NSCLC?

Recommendation	Grade
<p>In patients with inoperable stage I NSCLC and good performance status, high dose radiotherapy is an appropriate treatment option.</p> <p>Last reviewed November 2015</p>	<p><b>C</b></p>
<p>In patients with inoperable stage I NSCLC, high dose radiotherapy to a total of 60 Gy in 30 fractions over six weeks is a reasonable option. CHART may be used as an alternative to radical conventionally fractionated RT, provided the appropriate resources are available.</p> <p>Last reviewed November 2015</p>	<p><b>B</b></p>

### Point(s)

In patients with peripherally situated stage I NSCLC five cm or less in diameter, SABR is a reasonable treatment option. For larger tumours or those in less favourable anatomical sites close to organs at risk, it may be reasonable, for patient convenience, to moderately accelerate treatment e.g. 50-55Gy in 20 fractions (extrapolating from Price et al 2012).

Last reviewed November 2015

## 2.2.8 What is the role of radiofrequency ablation in stage I inoperable NSCLC?

### Point(s)

Further studies are required to define the efficacy and toxicities of radiofrequency ablation in the treatment of stage I NSCLC before its routine use can be recommended.

Last reviewed December 2015

There are several techniques available for thermal ablation of tumours of which RFA is one. The others are microwave and cryo-ablation.

Last reviewed December 2015

## Chemotherapy

### 2.2.9 What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage I NSCLC?

#### Point(s)

Insufficient evidence exists to recommend routine use of chemotherapy along with radiation for the treatment of patients with inoperable stage I NSCLC.

Last reviewed December 2015

Stage II operable  
Surgery

### 2.2.10 Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage II NSCLC?

#### Recommendation

A complete mediastinal lymph node dissection of at least Stations 2R, 4R, 7 and 8 (right side) or Stations 5, 6, 7 and 8 (left side) is recommended for surgically resected pathologically confirmed (node positive) stage II NSCLC.

Last reviewed November 2015

#### Grade

**B**

Radiotherapy

### 2.2.11 What is the role of radiotherapy after surgery in the treatment of operable stage II NSCLC?

#### Recommendation

In patients who have had complete resection of stage II NSCLC, postoperative radiotherapy is not recommended.

Last reviewed December 2015

#### Grade

**A**

Chemotherapy

### 2.2.12 What is the role of chemotherapy before surgery in the treatment of operable stage II NSCLC?

Recommendation	Grade
<p>Chemotherapy before surgery may be considered as an option for patients with operable stage II NSCLC.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>Chemotherapy before surgery in operable stage II disease, with 3-4 cycles of platinum-based regimens, may be considered in select patients, who are unlikely to receive it as adjuvant therapy.</p> <p>Last reviewed December 2015</p>	<b>B</b>

#### Point(s)

No benefit in improved operability rates has been demonstrated in using chemotherapy before surgery. Survival benefit of chemotherapy seem to be similar when given either before or after surgery. Chemotherapy before surgery may be considered for those patient who are expected to have prolonged delay in surgery.

Last reviewed December 2015

### 2.2.13 What is the role of chemotherapy after surgery in the treatment of operable stage II NSCLC?

Recommendation	Grade
<p>Patients with completely resected stage II NSCLC should be offered 3-4 cycles of adjuvant cisplatin based chemotherapy.</p> <p>Last reviewed December 2015</p>	<b>A</b>

#### Point(s)

The chemotherapy combination of cisplatin and vinorelbine was the most widely studied regimen which showed benefit.

**Point(s)**

Last reviewed December 2015

There is insufficient evidence to support adjuvant chemotherapy for patients with ECOG performance status of  $\geq 2$ .

Last reviewed December 2015

No recommendation can be made for patients who have had less than a lobectomy.

Last reviewed December 2015

Based on the 7th edition of TNM classification tumour size of  $>5\text{cm}$  would fall under stage IIA. These patients may be considered for adjuvant chemotherapy.

Last reviewed December 2015

Chemotherapy benefit is seen even in patients who have received radiotherapy as part of loco-regional therapy in addition to surgery.

Last reviewed December 2015

Potential long term side effects need to be considered while deciding on chemotherapy after surgery.

Last reviewed December 2015

Stage II inoperable

Radiotherapy

### 2.2.14 What is the best practice radiotherapy approach in patients with stage II inoperable NSCLC?

**Point(s)**

Patients with inoperable stage II disease could be offered radiotherapy with curative intent with or without concomitant chemotherapy.



**Point(s)**

Last reviewed November 2015

Chemotherapy

**2.2.15 What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage II NSCLC?**

**Recommendation**

Insufficient evidence exists to recommend routine use of chemotherapy along with radiation for the treatment of patients with inoperable stage II NSCLC.

Last reviewed August 2015

**Grade**

**C**

**Point(s)**

Patients with inoperable stage II disease could be offered radiotherapy with curative intent.

Patients with good performance status and organ function may be considered for definitive concurrent chemo-radiation with a platin-based regime. This has to be balanced with an increased risk of toxicity. This is based on data extrapolated from studies mainly including inoperable stage III disease.

Last reviewed August 2015

Stage III operable

Radiotherapy

**2.2.16 What is the role of postoperative radiotherapy (PORT) in resected stage III NSCLC?**

**Recommendation**

Post-operative radiation therapy in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. The use of PORT could be considered in selected patients with pN2 disease.

Last reviewed December 2015

**Grade**

**C**

**Point(s)**

Post-operative radiation therapy may be considered in the setting of a positive margin.

Last reviewed December 2015

Surgery

2.2.17 What is the clinical benefit of mediastinal lymph node dissection in stage IIIA operable NSCLC?

**Recommendation**

A complete mediastinal lymph node dissection of at least Stations 2R, 4R, 7 and 8 (right side) or Stations 5, 6, 7 and 8 (left side) is recommended for surgically resected pathologically confirmed (mediastinal node positive) stage IIIA NSCLC.

Last reviewed November 2015

**Grade**

**B**

2.2.18 What is the clinical benefit of the addition of surgery to definitive chemoradiotherapy in stage IIIA (N2) NSCLC?

**Recommendation**

Unselected patients with biopsy confirmed stage IIIA (N2) disease are best treated with chemoradiotherapy alone.

Last reviewed December 2015

**Grade**

**B**

**Point(s)**

Induction chemoradiotherapy followed by surgery in selected patients with cIIIA (N2) disease is feasible and improves progression-free survival. Provided the patient does not require a pneumonectomy, the addition of surgery may improve overall survival.

Last reviewed December 2015

Chemotherapy

### 2.2.19 What is the clinical benefit of adjuvant chemotherapy for patients with stage III operable NSCLC?

Recommendation	Grade
<p>Patients who have a good performance status (WHO 1, 2) and completely resected stage III non-small cell lung cancer should be offered adjuvant cisplatin-based chemotherapy.</p> <p>Last reviewed December 2015</p>	<b>A</b>
<p>Patients with superior sulcus NSCLC may be considered for induction chemoradiotherapy.</p> <p>Last reviewed December 2015</p>	<b>C</b>

#### Point(s)

Caution is advised in recommending adjuvant cisplatin-based chemotherapy to good performance status patients who are 70 years of age or older and/or who have clinically significant cardio-respiratory or renal co-morbidities.

Last reviewed December 2015

Patients with resectable stage III non-small cell lung cancer, who are being considered for preoperative chemotherapy and surgery or surgery and postoperative chemotherapy, should have their treatment plan reviewed in a lung cancer-specific multidisciplinary meeting. The recommended treatment plan may need to be individualized to take account of such patient-specific factors as treatment preference, availability and timing of surgery, and geographically remote location.

Last reviewed December 2015

### 2.2.20 What is the clinical benefit of neoadjuvant chemotherapy for patients with stage III operable NSCLC?

Recommendation	Grade
<p>It is recommended to consider pre-operative administration of 2-3 cycles of platinum doublet-based, third-generation chemotherapy as a treatment option in good performance status patients with operable clinical stage IIIA non-small cell lung cancer.</p>	<b>A</b>

Recommendation	Grade
Last reviewed December 2015	
<b>Point(s)</b>	
<p>Patients whose tumours respond to preoperative chemotherapy may derive additional survival benefit from postoperative chemotherapy.</p> <p>Last reviewed December 2015</p>	
<p>Patients with resectable stage III non-small cell lung cancer, who are being considered for preoperative chemotherapy and surgery or surgery and postoperative chemotherapy, should have their treatment plan reviewed in a lung cancer-specific multidisciplinary meeting. The recommended treatment plan may need to be individualized to take account of such patient-specific factors as treatment preference, availability and timing of surgery, and geographically remote location.</p> <p>Last reviewed December 2015</p>	
<p><b>2.2.21 What is the clinical benefit of the addition of neoadjuvant radiotherapy to neoadjuvant chemotherapy in stage IIIA (N2) NSCLC?</b></p>	
Recommendation	Grade
<p>In selected patients (excellent performance status and cardio respiratory reserve) with stage cIIIA (N2) NSCLC, planned for surgery that will entail less than pneumonectomy, it is reasonable to offer neoadjuvant chemoradiotherapy.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>
<b>Point(s)</b>	
<p>Surgery alone is not advised in cIIIA (N2) disease.</p> <p>Last reviewed December 2015</p>	
<p>Stage III inoperable Radiotherapy</p>	

### 2.2.22 What is the recommended treatment approach for the definitive management of patients with good performance status and inoperable stage III disease?

Recommendation	Grade
<p>For patients with good performance status and inoperable stage III NSCLC, the concurrent administration of chemotherapy and radiotherapy is recommended.</p> <p>Last reviewed December 2015</p>	<p><b>A</b></p>

Point(s)
<p>In stage III NSCLC patients deemed inoperable at the time of diagnosis, the recommended treatment approach is concurrent chemoradiotherapy. Evidence suggests that the optimal chemotherapy regimen to give concurrently with radiation therapy is a platinum-based doublet.</p> <p>Last reviewed December 2015</p>
<p>In patients with good performance status and inoperable stage III NSCLC in whom chemotherapy is contra-indicated, treatment with a radical dose of radiation therapy alone is a reasonable option.</p> <p>Last reviewed December 2015</p>

### 2.2.23 What is the optimal radiation dose and fractionation schedule for good performance status patients with inoperable stage III NSCLC undergoing curative therapy?

Recommendation	Grade
<p>It is recommended that for patients with inoperable stage III NSCLC undergoing curative therapy once daily thoracic radiotherapy to at least 60Gy in 2Gy/f plus chemotherapy is administered.</p> <p>Last reviewed December 2015</p>	<p><b>B</b></p>
<p>For patients with stage III NSCLC who are suitable for curative therapy, but where chemotherapy is contra-indicated or refused, CHART may be used as an alternative to radical conventionally fractionated radiotherapy.</p>	<p><b>B</b></p>

Recommendation	Grade
Last reviewed December 2015	
<p>2.2.24 What are the principles of radiation therapy in the definitive management of stage III inoperable NSCLC?</p>	
Recommendation	Grade
<p>Patients can be simulated in the treatment position using an immobilisation device.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>
<p>Treatment planning utilising multi-slice CT image acquisition and a 3D planning system is encouraged.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>
<p>The appropriate window settings may be used when contouring the parenchymal and nodal disease.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>
<p>Tumour volume delineation may be assisted by the incorporation of FDG-PET information into the CT -based planning system.</p> <p>Last reviewed December 2015</p>	<p><b>B</b></p>
<p>Tumour volume delineation may be assisted by the use of intravenous contrast during simulation.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>
<p>The Clinical Target Volume may encompass the Gross Tumour Volume plus a margin of 6-8mm.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>

Recommendation	Grade
<p>Elective nodal irradiation is not recommended.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>
<b>Point(s)</b>	
<p>Treatment planning may utilise an accepted method of evaluating and accounting for tumour motion.</p> <p>Last reviewed December 2015</p>	
<p>Individual characteristics of breathing and variations associated with tumour location and pulmonary and tumour pathology lead to individual patterns of tumour motion.</p> <p>Last reviewed December 2015</p>	
<p>-The Gross Tumour Volume may encompass the visible disease (both primary and nodal) on CT and/or CT-PET.</p> <p>-The Clinical Target Volume may encompass the Gross Tumour Volume plus a margin to account for microscopic extension of disease .</p> <p>-The Planning Target Volume may encompass the Clinical Target Volume plus a margin to account for tumour motion (as determined by the individual institution’s method of evaluating and accounting for tumour motion) and a margin to account for set-up error (as determined by the individual institutions’ estimation of the specific errors inherent in their process of radiotherapy planning and delivery).</p> <p>Last reviewed December 2015</p>	
<p><b>Normal Tissue Dose Volume Constraints</b></p> <p>Limiting the lung V20 ≤ 30-35% and the MLD ≤20-23Gy limits the risk of radiation pneumonitis to ≤20% in definitely treated patients with NSCLC.</p> <p>Lung: V20 ≤ 30 -35% , Mean total lung dose (MLD) ≤ 20-23Gy</p> <p>A total dose of 50Gy in 2Gy/f to the full spinal cord cross-section is associated with a 0.2% risk of myelopathy.</p> <p>Spinal Cord: 50Gy in 1.8-2.0Gy/f</p> <p>Last reviewed December 2015</p>	
<p>A single best threshold volumetric parameter for oesophageal irradiation has not been identified.</p>	

**Point(s)**

Last reviewed December 2015

2.2.25 What is the optimal treatment approach for patients with stage III inoperable NSCLC who, because of patient or tumour factors, are not suitable for curative treatment with concurrent chemo-radiotherapy and who do not have a mutation for targeted therapy?

Recommendation	Grade
<p>The patient's performance status should be taken into consideration when choosing the radiation dose and fractionation pattern:</p> <ul style="list-style-type: none"> <li>- Consider treating patients with good performance status with longer radiotherapy regimens because this will lead to a longer duration of symptom relief and may increase survival. Commonly employed radiotherapy regimens include 20Gy/5f, 30Gy/10f, 36Gy/12f, 40Gy/15f, 50Gy/20f.</li> <li>- Patients with poor performance status should be treated with short courses of treatment. Commonly employed radiotherapy regimens include 10Gy/1f, 16Gy/2f (1f/week).</li> </ul> <p>Last reviewed December 2015</p>	<b>A</b>
<p>For patients with stage III disease who because of performance status or disease extent are not suitable for treatment with curative intent and who are not experiencing symptoms specifically related to chest disease, referral for systemic therapy is recommended.</p> <p>Last reviewed December 2015</p>	<b>A</b>
<p>For patients with locally advanced, inoperable Stage III NSCLC not fit for curative therapy, consideration should be given to concurrent administration of palliative chemoradiation.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>For patients with stage III disease who because of performance status or disease extent are not suitable for treatment with curative intent and who are experiencing symptoms as a result of chest disease, palliative radiotherapy is recommended.</p> <p>Last reviewed December 2015</p>	<b>A</b>



**Point(s)**

Given the symptomatology experienced by these patients with stage III disease and their poor survival outcomes, referral to palliative care services should be considered.

Last reviewed December 2015

**2.2.26 What is the role of prophylactic cranial irradiation (PCI) in patients with stage III NSCLC?**

**Recommendation**

**Grade**

In patients with stage III NSCLC, the use of prophylactic cranial irradiation is not recommended.

**B**

Last reviewed December 2015

**2.2.27 What is the optimal management of Pancoast tumours?**

**Recommendation**

**Grade**

In patients deemed technically and medically fit for surgical resection, pre-operative concurrent chemoradiation followed by surgery is an acceptable treatment option for patients with Pancoast tumours.

**C**

Last reviewed December 2015

For patients with unresectable Pancoast tumours and good performance status, the concurrent administration of chemotherapy and radiotherapy is recommended.

**A**

Last reviewed December 2015

For patients who have a poor performance status or distant metastatic disease, radiation therapy can be used to palliate symptoms due to Pancoast tumour.

**C**

Last reviewed December 2015

Stage IV operable  
Radiotherapy

2.2.28 What is the clinical benefit of adjuvant whole brain radiotherapy following resection or stereotactic radiosurgery to the brain metastasis(es)?

Recommendation	Grade
<p>Routine adjuvant whole brain radiotherapy is not recommended following surgical resection or radiosurgery for brain metastases.</p> <p>Last reviewed September 2015</p>	<p><b>A</b></p>

Surgery

2.2.29 What is the optimal management of malignant pleural effusions?

Recommendation	Grade
<p>Consider using larger bore intercostal catheters for bedside pleurodesis, however smaller-bore, 12-14F, intercostal catheters may be used for bedside pleurodesis in patients with malignant pleural effusions.</p> <p>Last reviewed January 2017</p>	<p><b>B</b></p>
<p>Indwelling pleural catheters might be effective in the outpatient management of malignant pleural effusion.</p> <p>Last reviewed January 2017</p>	<p><b>C</b></p>
<p>Consider the use of an Indwelling pleural catheter in malignant pleural effusion caused by Haematological malignancies</p> <p>Last reviewed January 2017</p>	<p><b>D</b></p>
<p>VATS talc pleurodesis is recommended in fit (ECOG 0-2) patients with NSCLC with an expected survival of &gt;2 months who have &gt;90% lung expansion after needle thoracocentesis.</p> <p>Last reviewed January 2017</p>	<p><b>A</b></p>
<p>VATS talc pleurodesis may be considered in fit (ECOG 0-2) patients with NSCLC with an expected survival of &gt;2 months who have &lt;90% lung expansion after needle thoracocentesis.</p>	<p><b>C</b></p>

Recommendation	Grade
<p>VATS with biopsy and subsequent talc pleurodesis may be considered in patients who require pathological confirmation of their cancer to determine management.</p> <p>Last reviewed January 2017</p>	
<p>Intrapleural Hyperthermic Perfusion Chemotherapy (HIPEC) could be used in the treatment of malignant pleural effusions.</p> <p>Last reviewed January 2017</p>	<b>C</b>
<p>Intercostal catheter (ICC) pleurodesis should be performed in patients unfit for more aggressive interventions and is an acceptable alternative where access to VATS without delay is problematic.</p> <p>Last reviewed January 2017</p>	<b>A</b>
<p>Consider the use of radiofrequency ablation in addition to thoracoscopic pleurodesis in MPE from NSCLC for improved survival.</p> <p>Last reviewed January 2017</p>	<b>D</b>

Point(s)
<p>If attempting a talc slurry pleurodesis, consider using a large-bore intercostal catheter (24F) over a small-bore intercostal catheter (12-14F).</p> <p>Last reviewed January 2017</p>
<p>For fit patients, with an established diagnosis, an attempt to reduce pleural fluid re-accumulation by pleurodesis can be made at the first opportunity.</p> <p>Last reviewed January 2017</p>
<p>Initial drainage of MPE to dryness is a reasonable approach, as it may stratify patients to further treatment based on:</p> <p>a. radiological evidence of re expansion versus trapped lung, b. symptomatic improvement, and c. cytological confirmation of the diagnosis.</p> <p>Last reviewed January 2017</p>

**Point(s)**

Tunnelled pleural catheters (TPC) may be preferred where lung reinflation is not achieved, but consideration of the practicalities of ongoing care should be made before their use.

Last reviewed January 2017

Tunnelled pleural catheters may be considered in patients well enough for only a minor procedure where issues of disposable equipment costs can be addressed and ongoing clinical care is available.

Last reviewed January 2017

Long term pleural catheter may be an option in those patients who prefer this.

Last reviewed January 2017

In highly selected cases where re expansion is poor and patients adamantly refuse long term drainage, or alternatively have minimal symptomatic relief with drainage, it may be reasonable to attempt VATS decortication.

Last reviewed January 2017

VATS decortication cannot be justified in patients with symptomatic relief from long term catheter drainage despite poor lung expansion.

Last reviewed January 2017

Insertion of a small intercostal catheter is not without risk. In particular, standard dilators are long enough to damage major mediastinal structures if inserted an unnecessary distance into the thoracic cavity.

Last reviewed January 2017

Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) are noninferior to opiates for pleurodesis failure, although more rescue analgesia is required

Last reviewed January 2017

### 2.2.30 What is the clinical benefit of resection of brain metastasis?

Recommendation	Grade
<p>In the absence of impending neurological emergency or the requirement of histological confirmation, patients with brain metastases may be managed with WBRT alone.</p> <p>Last reviewed December 2015</p>	<p><b>B</b></p>
<p>In younger patients, with good performance status and solitary brain metastasis or single brain metastasis and control of extra cranial disease, addition of surgery to WBRT is a reasonable approach.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>

Point(s)
<p>Surgery may control symptoms more quickly than WBRT and is reasonable in cases of impending neurological emergency.</p> <p>Last reviewed December 2015</p>
<p>Surgery provides histological confirmation and is reasonable in cases where the aetiology of the brain lesions is in question or histological information is not available from the primary tumour.</p> <p>Last reviewed December 2015</p>
<p>In cases of multiple metastases, addition of surgery to WBRT may be reasonable for rapid symptom control or for histological confirmation.</p> <p>Last reviewed December 2015</p>
<p>In cases of multiple metastases, addition of surgery to WBRT may be reasonable in highly individualised cases with the goal of improvement in local control, overall survival or FIS.</p> <p>Stereotactic radiosurgery may be an alternative to surgery in these patients.</p> <p>Last reviewed December 2015</p>

### 2.2.31 What is the clinical benefit of resection of primary disease after complete resection of metastatic disease?

#### Point(s)

In highly selected patients with T1-3 N0-1 lung cancers with good performance status, adequate pulmonary reserve and solitary site of metastasis, it may be reasonable to consider resection of primary and metastatic sites.

Last reviewed December 2015

It is advisable to consider only those patients who would require less than pneumonectomy and with T 1-3, N0-1 NSCLC for resection of primary and metastatic sites.

Last reviewed December 2015

Stage IV inoperable  
Radiotherapy

### 2.2.32 What is the clinical benefit of radiotherapy to the brain for patients with inoperable brain metastases from NSCLC?

#### Recommendation

#### Grade

Patients with multiple brain metastases from lung cancer who have good prognostic factors, based on prognostic models, should be considered for whole brain radiotherapy.

**A**

Last reviewed December 2015

For patients with multiple metastases a dose of 20Gy in 5 fractions or 30Gy in 10 fractions is adequate for palliation of symptoms and improvement in neurological function.

**B**

Last reviewed December 2015

Patients with multiple brain metastases from lung cancer who have adverse prognostic factors, based on prognostic models, should be considered for best supportive care including steroids.

**B**

Last reviewed December 2015

### 2.2.33 What is the role of stereotactic radiosurgery in the treatment of brain metastases?

Recommendation	Grade
<p>Patients with one to three unresectable brain metastases and stable systemic disease may be considered for a stereotactic radiosurgery boost in addition to whole brain radiotherapy.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>
<p>Radiosurgery may be used as an alternative to surgery for patients with one to three brain metastases and stable systemic disease.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>

#### Point(s)

The study on which the above recommendation is based prescribed whole brain radiotherapy for all patients. However routine adjuvant whole brain radiotherapy is no longer recommended following surgical resection or radiosurgery for brain metastases.

Last reviewed December 2015

### 2.2.34 What is the clinical benefit of radiotherapy to the bone for metastatic disease from NSCLC?

Recommendation	Grade
<p>Patients who have pain from bony metastases (not at risk of pathological fracture) should be offered palliative radiotherapy.</p> <p>Last reviewed December 2015</p>	<p><b>A</b></p>
<p>A single fraction of 8Gy is recommended if the clinical endpoint is pain relief.</p> <p>Last reviewed December 2015</p>	<p><b>A</b></p>
<p>Patients who have had orthopaedic fixation of a pathological fracture may be considered for adjuvant radiotherapy.</p> <p>Last reviewed December 2015</p>	<p><b>C</b></p>

**Point(s)**

Patients at risk of pathological fracture should be referred for prophylactic fixation prior to radiotherapy. The Mirel score is a useful tool in assessing this but patient factors should also be taken into account.

Last reviewed December 2015

**2.2.35 What is the clinical benefit of radiotherapy in metastatic spinal cord compression?**

**Recommendation**

**Grade**

Patients who have spinal cord compression from metastatic cancer should be considered for radiotherapy, either as primary treatment or following surgery.

**B**

Last reviewed November 2015

Recommended radiotherapy doses for patients treated with radiotherapy alone are 8-20Gy in 1-5 fractions.

**B**

Last reviewed November 2015

**Point(s)**

Patients with spinal cord compression may be commenced on dexamethasone 4-16mg a day to reduce oedema around the spinal cord. This can be weaned once treatment is complete.

Last reviewed November 2015

Spinal stability should be assessed in patients with spinal cord compression. The SINS score is a useful tool to assess this but patient factors should also be taken into account.

Last reviewed November 2015

**Chemotherapy**



### 2.2.36 What is the optimal systemic therapy for stage IV inoperable NSCLC?

Recommendation	Grade
Platinum-based chemotherapy can be used to palliate disease symptoms and extend survival in newly diagnosed patients with stage IV NSCLC	<b>A</b>
First-line combination chemotherapy should in most cases be stopped at disease progression or after four cycles in patients with advanced NSCLC.	<b>B</b>
High dose bevacizumab (15 mg/kg three-weekly) may be considered in addition to chemotherapy (carboplatin/paclitaxel or cisplatin/gemcitabine) in carefully selected** patients with non-squamous cell carcinoma.	<b>B</b>
The first generation EGFR TKIs gefitinib or erlotinib should not be used in unselected patients in combination with standard chemotherapy.	<b>A</b>
In patients with whose tumours have been shown to express EGFR by immunohistochemistry, cetuximab may be considered in addition to cisplatin/vinorelbine chemotherapy to improve response rate and overall survival.	<b>B</b>
In unselected patients with stable or responsive advanced NSCLC after four cycles of initial platinum doublet chemotherapy, “switch maintenance” therapy to an alternative agent is recommended to delay tumour progression. Options in unselected patients include erlotinib or docetaxel, whilst in patients with non-squamous cell carcinoma histology, pemetrexed.	<b>A</b>
In unselected patients previously treated for advanced NSCLC, chemotherapy with docetaxel or pemetrexed may be used as second-line therapy. Pemetrexed is preferred in non-squamous cell carcinoma histology, and docetaxel is preferred in squamous cell carcinoma.	<b>B</b>
In unselected patients previously treated for advanced NSCLC, gefitinib 250 mg per day orally or erlotinib 150 mg per day orally can be used as second-line therapy, instead of chemotherapy.	<b>B</b>
Doublet therapy is not recommended as second-line treatment of advanced NSCLC .	<b>A</b>
In unselected patients having previously received two lines of treatment for advanced NSCLC, erlotinib 150 mg per day orally can be used as third- line therapy.	<b>B</b>
First-line monotherapy with 3G chemotherapy could be offered to selected patients with PS2 for symptom improvement and possible survival gain, who are willing to accept treatment toxicity.	<b>B</b>
In patients with high tumour burden and symptoms from stage IV NSCLC cisplatin based	<b>B</b>

Recommendation	Grade
chemotherapy may be used in preference to carboplatin for the purpose of inducing a response, however, this benefit may be offset by its greater risk of toxicity.	
Poor performance status patients having received 1 or 2 lines of prior therapy, may be offered erlotinib 150 mg daily.	<b>B</b>
Suitably fit patients over 65 years of age, can be offered first-line mono-chemotherapy with a 3G single agent (vinorelbine (25-30 mg/ m <sup>2</sup> Day one, eight Q3 weekly), docetaxel (60 mg /m <sup>2</sup> (day one, Q3 weekly) or gemcitabine (1150 mg/m <sup>2</sup> days one and eight, Q3 weekly).	<b>B</b>
In elderly patients, first-line gemcitabine doublet chemotherapy is not recommended.	<b>B</b>
In fit elderly patients, first-line carboplatin/weekly paclitaxel may be offered instead of 3G monotherapy but at the expense of greater neutropenia.	<b>B</b>
Due to the therapeutic implications, it is important to classify the histologic subtype of NSCLC on diagnostic specimens as accurately as possible, particularly to enable accurate distinction between the key histologic subtypes: adenocarcinoma and squamous cell carcinoma.	<b>A</b>
Patients with known activating gene mutations (exon-19 deletions or exon-21 point mutations) to EGFR should be treated with an EGFR TKI.	<b>A</b>
Where EGFR mutation status is negative or unknown, patients should be treated with standard chemotherapy.	<b>B</b>
3G platinum-based chemotherapy (with vinorelbine, paclitaxel, docetaxel or gemcitabine) is a standard of care as first-line chemotherapy in fit patients with stage IV NSCLC.	<b>A</b>
In the first-line setting, chemotherapy with cisplatin and pemetrexed is recommended in preference to cisplatin and gemcitabine in patients with non-squamous cell carcinoma histology.	<b>B</b>
In the first-line setting, chemotherapy with cisplatin and gemcitabine is recommended in preference to cisplatin and pemetrexed in patients with squamous cell carcinoma histology.	<b>B</b>
Patients fit for chemotherapy should be offered 3G platinum-based combination chemotherapy (vinorelbine, paclitaxel, docetaxel, irinotecan or gemcitabine) in preference to 3G agent monotherapy, as it is more effective.	<b>A</b>
Patients unfit for combination chemotherapy could be considered for 3G monotherapy with vinorelbine, paclitaxel, docetaxel or gemcitabine.	<b>A</b>
Triplet chemotherapy regimens are not recommended, as benefit in response rate does not	

Recommendation	Grade
outweigh extra toxicity.	<b>A</b>
Non-platinum 3G doublet chemotherapy is an effective alternative option for patients unsuitable for platinum-based therapy.	<b>B</b>

Point(s)
<p>The decision to undertake empirical platinum-based chemotherapy in a given patient should consider factors such as patient performance status (0,1 versus 2 or more) and co-morbidities, their disease extent and symptoms, proposed treatment toxicity and their individual preferences for benefit from specific treatment(s) and toxicities.</p>
<p>The choice of cisplatin versus carboplatin in a given patient may consider the balance between perceived benefit (in tumour response) versus known toxicity, whilst considering patient preferences.</p>
<p>The choice of first-line platinum combination chemotherapy in a given patient may consider patient performance status and co-morbidities, the proposed treatment toxicity, treatment scheduling and individual patient preferences.</p>
<p>The duration of first-line chemotherapy in a given patient in practice may be based on the benefit being obtained in terms of tumour response, the desire to delay tumour progression and improve or maintain quality of life balanced against treatment toxicity. In practice maximum benefit from first-line chemotherapy has usually been obtained by four cycles of treatment.</p>
<p>As overall quality of life does not seem to differ across the different chemotherapy regimens, the choice of chemotherapy in an individual patient may involve discussion regarding expected toxicities and the patient's preferences.</p>
<p>Decision-making on treatment in poor performance status patients may weigh up benefits against toxicity and patient preferences. Whilst a single agent 3G chemotherapy is an option in unselected patients, patients with known activating EGFR MTs should be considered for first line EGFR TKIs as the magnitude of benefit is greater and toxicity profile more favourable.</p>
<p>Given the importance of accurate histologic diagnosis and the potential need to have sufficient tissue for subsequent molecular testing, it is important to obtain as much tissue as possible at initial diagnosis in patients suspected to have NSCLC.</p>
<p>A multidisciplinary team discussion may be required in order to decide on the most appropriate diagnostic method to obtain adequate tissue.</p>
<p>The evidence in support of large treatment benefits with first line EGFR TKIs in RR and PFS argues for consideration of obtaining adequate tumour tissue where possible, to enable molecular testing for the presence of activating EGFR gene mutations. This will enable clinicians to offer patients initial EGFR TKIs</p>

**Point(s)**

versus empirical therapy, bearing in mind that overall survival for EGFT GMT + patients does not appear to be compromised as long they go on to receive EGFR TKIs after chemotherapy.

## 2.3 Small cell lung cancer

Limited stage  
Chemotherapy

### 2.3.1 What is the optimal systemic therapy and duration to be used for the treatment of limited stage small cell lung cancer?

Recommendation	Grade
Platinum-etoposide regimens are considered the standard systemic chemotherapy in the treatment of limited stage small cell lung cancer.  Last reviewed November 2015	<b>B</b>
Therapy beyond the standard four cycles of induction chemotherapy cannot be recommended.  Last reviewed November 2015	<b>A</b>

**Point(s)**

It is advisable to use platinum plus etoposide for four cycles in patients with limited stage small cell lung cancer.

Last reviewed November 2015

### 2.3.2 What is the optimal concurrent chemotherapy to be used for the treatment of limited stage small cell lung cancer with radiotherapy?

Recommendation	Grade
Platinum plus etoposide is recommended as the chemotherapy backbone for concurrent chemoradiotherapy in patients with limited stage small cell lung cancer.	<b>B</b>

Recommendation	Grade
Last reviewed August 2015	

Point(s)
<p>It is advisable to use three-weekly platinum and etoposide chemotherapy during concurrent chemoradiotherapy for limited stage small cell lung cancer.</p> <p>Chest irradiation is optimally commenced early during the course of chemotherapy.</p> <p>Last reviewed August 2015</p>

Radiotherapy

### 2.3.3 Which patients with SCLC benefit from prophylactic cranial irradiation?

Recommendation	Grade
<p>Patients with limited stage and a complete response to initial therapy, and patients with extensive stage and stage who do not receive MRI brain and any response to initial therapy, should be offered prophylactic cranial irradiation.</p> <p>Last reviewed September 2017</p>	<b>A</b>

Point(s)
<p>Although there is no high level data to directly support the practice of prophylactic cranial irradiation in SCLC limited stage patients who achieve a partial response to initial therapy, the benefits of such practice may be inferred from randomised data in SCLC extensive stage patients. Prophylactic cranial irradiation may, therefore, be considered for patients with limited stage SCLC who are partial responders to initial therapy.</p> <p>Last reviewed September 2017</p>
<p>It is appropriate to obtain a brain CT scan before embarking on prophylactic cranial irradiation, to exclude pre-existing brain metastases. If brain metastases are detected then a palliative rather than prophylactic dose of whole brain radiotherapy may be delivered. MRI brain is preferable where available, as PCI may be avoided in those ES patients without brain metastases on MRI.</p> <p>Last reviewed September 2017</p>

### 2.3.4 What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with limited stage SCLC?

Recommendation	Grade
<p>Patients with limited stage small cell lung cancer achieving a complete response to initial therapy should receive prophylactic cranial irradiation to a dose of 25Gy in 10 daily fractions.</p> <p>Last reviewed September 2017</p>	<b>B</b>

### 2.3.5 What is the optimal timing of thoracic radiotherapy in patients receiving chemotherapy for limited stage SCLC?

Recommendation	Grade
<p>Fit patients with limited stage small cell lung cancer should receive thoracic radiotherapy concurrently with the first cycle of chemotherapy or as soon as possible thereafter.</p> <p>Last reviewed September 2017</p>	<b>B</b>

Point(s)
<p>It is desirable not only to institute radiotherapy as soon as possible, but also to complete it as soon as possible, ideally within 30 days.</p> <p>Last reviewed September 2017</p>

### 2.3.6 What is the optimal dose and fractionation schedule of thoracic radiotherapy in patients with limited stage SCLC?

Recommendation	Grade
<p>For patients with good performance status receiving chemotherapy for limited stage small cell lung cancer, the concurrent administration of twice daily radiotherapy to a dose of 45Gy in 30 twice-daily fractions is recommended.</p> <p>Last reviewed August 2017</p>	<b>B</b>

**Point(s)**

When following the accelerated hyperfractionated regimen of Turrisi et al, normal tissue tolerance limits specific to this protocol should be observed and a minimum interval of six hours between fractions should be ensured.

Last reviewed August 2017

If resource or other limitations preclude the delivery of twice-daily thoracic radiotherapy then daily radiotherapy should be delivered to a high dose. Pending the results of ongoing trials, doses in the range of 54Gy-60Gy in 27-30 fractions are reasonable provided acceptable dose constraints can be met. If a hypofractionated regimen is desired, then 40Gy in 15 daily fractions may be chosen as good quality toxicity and survival data have been published for this schedule.

Last reviewed August 2017

### 2.3.7 What is the optimal treatment volume in patients with limited stage SCLC receiving thoracic radiotherapy?

Recommendation	Grade
<p>Where radiotherapy is delivered after chemotherapy has begun, radiotherapy target volumes should be based on the post-chemotherapy volume of disease. Radiotherapy should be delivered to all originally involved nodal regions irrespective of their response to chemotherapy.</p> <p>Last reviewed September 2017</p>	<b>B</b>
<p>Elective nodal irradiation may be omitted to reduce toxicity.</p> <p>Last reviewed September 2017</p>	<b>C</b>

**Point(s)**

In the setting of SCLC, positron emission tomography (PET) appears useful both for staging as well as for the definition of radiotherapy volumes. Where available, information from PET scans should be incorporated into radiotherapy target definition.

**Point(s)**

Last reviewed September 2017

Extensive stage  
Chemotherapy

**2.3.8 What is the optimal chemotherapy regimen and duration of therapy in extensive stage small cell lung cancer in the first-line setting?**

Recommendation	Grade
<p>The platinum etoposide regimen is recommended as the first-line therapy for patients with extensive stage small cell lung cancer. Irinotecan-platinum may be an alternative in selected patients.</p> <p>Last reviewed December 2015</p>	<p><b>B</b></p>

**Point(s)**

It is advisable to consider the platinum etoposide regimen as first-line therapy in patients with extensive stage small cell lung cancer, treatment should continue for at least four to six cycles. Maintenance therapy provides no additional benefit.

Last reviewed December 2015

**2.3.9 What is the optimal second-line therapy in patients with extensive stage small cell lung cancer?**

Recommendation	Grade
<p>Topotecan or CAV are recommended as second-line therapy in patients with extensive stage small cell lung cancer who have chemotherapy responsive disease (i.e. relapse &gt; three months post first-line therapy).</p> <p>Last reviewed December 2015</p>	<p><b>A</b></p>

Radiotherapy



### 2.3.10 What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with extensive stage SCLC?

Recommendation	Grade
<p>For patients with extensive stage small cell lung cancer who achieve a response to initial therapy, a range of prophylactic cranial irradiation dose schedules from 20Gy in 5 fractions to 30Gy in 10 fractions is reasonable.</p> <p>Last reviewed November 2015</p>	<p><b>B</b></p>

Point(s)
<p>There is insufficient evidence to recommend a particular prophylactic cranial irradiation dose or fractionation schedule over any other. However, since extensive stage small cell lung cancer has a median survival of less than a year, a short fractionation schedule (20Gy in 5 fractions) is recommended for most patients.</p> <p>Last reviewed November 2015</p>

### 2.3.11 Is there a role for thoracic radiotherapy in patients with extensive stage SCLC?

Recommendation	Grade
<p>Strongly consider administering moderate dose consolidative chest radiotherapy (30 Gy in 10 fractions) to chemotherapy responders, especially those with residual disease in the thorax.</p> <p>Last reviewed December 2015</p>	<p><b>B</b></p>

Point(s)
<p>Chest radiotherapy was administered 6-7 weeks after chemotherapy and usually 1 week after completion of prophylactic cranial irradiation.</p> <p>Those patients with the heaviest extrathoracic metastatic burden and poor response to chemotherapy may be expected to benefit the least from thoracic radiotherapy. In addition, patients with no residual disease in the thorax after chemotherapy derived no benefit from consolidative thoracic radiotherapy in a post hoc analysis by Slotman et al.</p> <p>Last reviewed December 2015</p>

## 2.4 Palliative care

### 2.4.1 What is the role of palliative care in symptom management for patients with lung cancer?

Recommendation	Grade
<p>There is strong evidence from consistent randomised trials to support the use of NSAIDs and opioids for the management of pain in patients with NSCLC.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>There is a role for the use of bisphosphonates and radiopharmaceuticals in a select group of patients with pain arising from multiple site of bony metastasis.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>The use of opioids are recommended for the relief of dyspnoea in patients with NSCLC.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>Following individual patient assessment and a therapeutic trial, oxygen administered intranasally may be administered to patients with advanced lung cancer to palliate the symptom of breathlessness.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>Subcutaneous methylnaltrexone should be considered in patients where conventional laxatives have failed.</p> <p>Last reviewed December 2015</p>	<b>B</b>

#### Point(s)

- It is advised that the use of methadone occurs with involvement of specialist palliative care or pain services, due to its complex pharmacodynamic properties.

**Point(s)**

- The choice of opioids used may consider issues of availability, cost and individual patient factors such as route of administration, metabolism and organ impairment such as renal failure.
- Anticonvulsants such as gabapentin and pregabalin may be considered in the management of neuropathic pain, based on substantive body of evidence generated in non-cancer patients.
- Non-pharmacological approaches and complementary therapies may be considered as part of a multimodal approach when pain remains poorly controlled.

Last reviewed December 2015

The use of non-pharmacological strategies, such as breathing retraining, simple relaxation, activity pacing and psychosocial support from nursing or allied health, can be beneficial for the management of breathlessness.

Last reviewed December 2015

Benzodiazepines can be used as a second or third line therapy in the treatment of breathlessness in patients with advanced lung cancer, when opioids and non-pharmacological measures have failed.

Last reviewed December 2015

Recommendations for the treatment of constipation in the palliative care population have been made based on expert opinion and currently suggest a combination of stimulant and softening agent.

Last reviewed December 2015

- Centrally acting oral opioids may be considered for the suppression of cough in NSCLC
- Symptomatic treatment with antimuscuranic agents or antibiotics may be helpful by reducing the volume of secretions or mucopurulent sputum.
- Where appropriate and accessible, interventions such as brachytherapy may be beneficial for the management of cough in selected patients. (Refer to *Brachytherapy section in Radiotherapy Stage IV*)

Last reviewed December 2015

Palliative measures for the management of haemoptysis include the use of oral haemostatics e.g. tranexamic acid, or radiotherapy, or laser treatment to the tumour site and the active management of underlying causes, such as infection, or pulmonary infarction.

Last reviewed December 2015

## 2.4.2 What is the role of advance care planning and timing of referral for patients with lung cancer?

Recommendation	Grade
<p>It is recommended to refer patients with stage IV inoperable NSCLC to palliative care at the time of diagnosis of metastatic disease.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>Advance care planning discussions should be initiated with patients, as there are multiple benefits.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>Clinicians may explore patients' understanding of their health situation and offer to provide further information about their prognosis and to explore the patients' goals/priorities/fears and concerns about the future.</p> <p>Last reviewed December 2015</p>	<b>C</b>

Point(s)
<p>Consider referral to palliative care when metastatic disease is diagnosed. Don't wait until there is definite evidence of medical deterioration.</p> <p>Last reviewed December 2015</p>
<p>It may take some time for patients and their families to comprehend and process advance care planning discussions. Discussing patients understanding of their disease and/ or prognosis along with their hopes and fears may enable important conversations. It is never 'too early' to explore these concerns.</p> <p>Last reviewed December 2015</p>

## 2.4.3 What is the role of psychological support and interventions in the treatment of lung cancer?

Recommendation	Grade
	<b>B</b>

Recommendation	Grade
<p>Psycho-educational interventions including: counseling, behaviour therapy, education /information giving, and social support will assist in ameliorating the impact of depression.</p> <p>Last reviewed December 2015</p>	
<p>There is reasonable evidence from systematic reviews to support the use of Cognitive Behaviour Therapy (CBT) in the management of depression particularly in the short-term (in group or individual format). Further randomised controlled trials involving adequately powered studies and consistent methodology should be conducted.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>Cognitive Behaviour Therapy (CBT) is recommended for the treatment of anxiety in NSCLC. Further randomised controlled trials involving adequately powered studies and consistent methodology should be conducted.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>Supportive and Meaning based group psychotherapies, may be helpful in reducing anxiety in NSCLC patients. Further randomised controlled trials involving adequately powered studies and consistent methodology should be conducted.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>Psychological interventions including Cognitive Behaviour Therapy (CBT), education, self-care strategies, behavioural interventions, activity management, supportive psychotherapy have all been found to ameliorate fatigue.</p> <p>Further randomised controlled trials involving adequately powered studies and consistent methodology can be conducted to ascertain unmet needs in advanced cancer.</p> <p>Last reviewed December 2015</p>	<b>C</b>
<p>Psychological interventions have an important role in the management of cancer related pain.</p> <p>Last reviewed December 2015</p>	<b>B</b>
<p>Quality of life of lung patients may improve with behavioural, cognitive or social cognitive therapies.</p> <p>Last reviewed December 2015</p>	<b>C</b>
<p>Non-invasive nurse-led programs with a focus on managing physical symptoms and treatment related toxicities may be used to optimise quality of life.</p>	<b>C</b>

Recommendation	Grade
Last reviewed December 2015	

## 2.5 Supportive care

### 2.5.1 What is the role of case management in the treatment of patients with lung cancer?

Recommendation	Grade
<p>Lung cancer nurses should be involved in the follow-up care of patients with lung cancer in centres where there is a significant lung cancer case load.</p> <p>The model of implementation should be flexible.</p> <p>Last reviewed October 2015</p>	<b>B</b>

Point(s)
<p>The UK standard of 80% involvement of LCNS at the time of lung cancer diagnosis is not a rational one in Australia where lung cancer diagnosis is more de-centralised.</p> <p>With the above caveat, including a LCNS in the care of patients from early in the diagnosis-decision making stage may be highly valuable.</p> <p>By extension of the universal acceptance of the role of breast care nurses, it seems more than probable that patients with lung cancer would benefit in a similar fashion.</p> <p>Last reviewed October 2015</p>
<p>When a clinical problem develops, the threshold for a patient to contact a nurse is lower than that for contacting a doctor whom they often wish not to trouble.</p> <p>As lung cancer nurses are introduced to the Australian setting, careful planning will optimise the benefit in improved patient care.</p> <p>In the rural setting, the lung cancer case load may not be sufficient to justify a lung cancer specific nurse and the optimal plan. may be to increase educational standards of existing nurses with more general roles.</p> <p>Last reviewed October 2015</p>
<p>Lung cancer nurses can be integral to the care of patients with lung cancer in centres where there is a significant lung cancer case load.</p>

**Point(s)**

Last reviewed October 2015

**2.5.2 What is the role of topical creams, skin moisturisers and maintenance antibiotics in the treatment of rash from anti-EGFR therapy in patients with lung cancer?**

**Recommendation**

**Grade**

A tetracycline can be prescribed in conjunction with anti-EGFR therapy, as it may reduce the severity and frequency of rash.

**C**

Last reviewed September 2017

**Point(s)**

Rash is a common adverse effect and at the commencement of treatment, patients may be informed of this possibility.

Patients can be made aware that the severity of rash may be reduced by prophylactic antibiotic treatment.

Last reviewed September 2017

Patients may have reduced severity of skin rash by the addition of prophylactic skin moisturiser, however data suggesting frequency and product selection is lacking.

Last reviewed September 2017

Vitamin K cream can not be recommended for the purpose of reducing rash.

Last reviewed September 2017

Sunscreen cannot be recommended for the purpose of reducing rash. Barrier methods – clothing, hats and limiting time in the sun can be employed in preference.

Last reviewed September 2017

For very severe rash, alone or in combination with other skin adverse effects, treatment can be discontinued or suspended.

Last reviewed September 2017

Evidence for treatments supplementary to antibiotics for rash is presently lacking, but a useful effect cannot be disproven.

Last reviewed September 2017

Point(s)
<p>Topical formulations of steroids and tacrolimus do not add to the benefit of antibiotic treatment.</p> <p>Last reviewed September 2017</p>
<p>Anecdotal evidence supports the use of skin moisturisers but data for product selection, frequency of use and consequential outcomes are lacking.</p> <p>The routine use of moisturisers can be justified at the outset of EGFR-TKI but this is based on expert opinion and reasonable fear of the consequences of inaction not controlled trials.</p> <p>Severe drying with fissuring can be regarded as a serious complication and the opinion of a Dermatologist, ideally one with an interest in this clinical area, may be sought.</p> <p>Last reviewed September 2017</p>
<p>Patients with clinically significant rash may be commenced on oral antibiotic therapy with tetracycline, minocycline or doxycycline.</p> <p>Last reviewed September 2017</p>
<p>The treatment for paronychia is based on expert opinion as no randomised controlled trials have evaluated the therapies.</p> <p>The consensus of expert opinion suggests where there is no signs of infection, the topical application of a corticosteroid combined with a systemic cycline antibiotic.</p> <p>In severe cases and signs of infection, it is recommended to swab, treat with appropriate systemic antibiotic and refer to dermatologist.</p> <p>Last reviewed September 2017</p>

### 2.5.3 What is the optimal management of malignant pleural effusions?

Recommendation	Grade
<p>Consider using larger bore intercostal catheters for bedside pleurodesis, however smaller-bore, 12-14F, intercostal catheters may be used for bedside pleurodesis in patients with malignant pleural effusions.</p> <p>Last reviewed January 2017</p>	<b>B</b>
<p>Indwelling pleural catheters might be effective in the outpatient management of malignant pleural effusion.</p>	<b>C</b>



Recommendation	Grade
Last reviewed January 2017	
<p>Consider the use of an Indwelling pleural catheter in malignant pleural effusion caused by Haematological malignancies</p> <p>Last reviewed January 2017</p>	<b>D</b>
<p>VATS talc pleurodesis is recommended in fit (ECOG 0-2) patients with NSCLC with an expected survival of &gt;2 months who have &gt;90% lung expansion after needle thoracocentesis.</p> <p>Last reviewed January 2017</p>	<b>A</b>
<p>VATS talc pleurodesis may be considered in fit (ECOG 0-2) patients with NSCLC with an expected survival of &gt;2 months who have &lt;90% lung expansion after needle thoracocentesis.</p> <p>VATS with biopsy and subsequent talc pleurodesis may be considered in patients who require pathological confirmation of their cancer to determine management.</p> <p>Last reviewed January 2017</p>	<b>C</b>
<p>Intrapleural Hyperthermic Perfusion Chemotherapy (HIPEC) could be used in the treatment of malignant pleural effusions.</p> <p>Last reviewed January 2017</p>	<b>C</b>
<p>Intercostal catheter (ICC) pleurodesis should be performed in patients unfit for more aggressive interventions and is an acceptable alternative where access to VATS without delay is problematic.</p> <p>Last reviewed January 2017</p>	<b>A</b>
<p>Consider the use of radiofrequency ablation in addition to thoracoscopic pleurodesis in MPE from NSCLC for improved survival.</p> <p>Last reviewed January 2017</p>	<b>D</b>

**Point(s)**

If attempting a talc slurry pleurodesis, consider using a large-bore intercostal catheter (24F) over a small-bore intercostal catheter (12-14F).

**Point(s)**

Last reviewed January 2017

For fit patients, with an established diagnosis, an attempt to reduce pleural fluid re-accumulation by pleurodesis can be made at the first opportunity.

Last reviewed January 2017

Initial drainage of MPE to dryness is a reasonable approach, as it may stratify patients to further treatment based on:

- a. radiological evidence of re expansion versus trapped lung, b. symptomatic improvement, and c. cytological confirmation of the diagnosis.

Last reviewed January 2017

Tunnelled pleural catheters (TPC) may be preferred where lung reinflation is not achieved, but consideration of the practicalities of ongoing care should be made before their use.

Last reviewed January 2017

Tunnelled pleural catheters may be considered in patients well enough for only a minor procedure where issues of disposable equipment costs can be addressed and ongoing clinical care is available.

Last reviewed January 2017

Long term pleural catheter may be an option in those patients who prefer this.

Last reviewed January 2017

In highly selected cases where re expansion is poor and patients adamantly refuse long term drainage, or alternatively have minimal symptomatic relief with drainage, it may be reasonable to attempt VATS decortication.

Last reviewed January 2017

VATS decortication cannot be justified in patients with symptomatic relief from long term catheter drainage despite poor lung expansion.

Point(s)
<p>Last reviewed January 2017</p>
<p>Insertion of a small intercostal catheter is not without risk. In particular, standard dilators are long enough to damage major mediastinal structures if inserted an unnecessary distance into the thoracic cavity.</p> <p>Last reviewed January 2017</p>
<p>Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) are noninferior to opiates for pleurodesis failure, although more rescue analgesia is required</p> <p>Last reviewed January 2017</p>

[Back to top](#)

## 2.6 Levels of evidence and grades for recommendations

The following table provides a list of the evidence-based recommendations detailed in the content of each topic question. The table below provides details on the highest level of evidence identified to support each recommendation (I-IV). The Summary of Recommendations table includes the grade for each recommendation (A-D). The key references that underpin the recommendation are provided in the last column. Individual levels of evidence can be found in the Evidence Summaries for each recommendation in each question.

Each recommendation was assigned a grade by the expert working group taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence supporting each recommendation. When no Level I or II evidence was available and in some areas, in particular where there was insufficient evidence in the literature to make a specific evidence-based recommendation, but also strong and unanimous expert opinion amongst the working group members about both the advisability of making a clinically relevant statement and its content, recommended best practice points were generated. Thus, the practice points relate to the evidence in each question, but are more expert opinion-based than evidence-based. These can be identified throughout the guidelines with the following: Practice point (PP).

Grade of recommendation	Description
<b>A</b>	Body of evidence can be trusted to guide practice
<b>B</b>	Body of evidence can be trusted to guide practice in most situations
<b>C</b>	Body of evidence provides some support for recommendation(s) but care should be taken in its application
<b>D</b>	Body of evidence is weak and recommendation must be applied with caution

## Clinical practice guidelines for the treatment of lung cancer

Grade of recommendation	Description
<b>PP</b> (practice point)	Where no good-quality evidence is available but there is consensus among Guideline committee members, consensus-based guidance points are given, these are called "Practice points"

Adapted from: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.<sup>[1]</sup> ([https://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/developers/nhmrc\\_levels\\_grades\\_evidence\\_120423.pdf](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf))

Level of evidence was assigned according to the following criteria from the NHMRC Evidence Hierarchy<sup>[1]</sup>:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
<b>I</b>	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
<b>II</b>	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
<b>III-1</b>	A pseudo-randomised controlled trial (i. e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i. e. alternate allocation or some other method)
<b>III-2</b>	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>■ Non-randomised, experimental trial</li> <li>■ Cohort study</li> <li>■ Case-control study</li> </ul>	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>■ Non-randomised, experimental trial</li> <li>■ Cohort study</li> </ul>

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
	<ul style="list-style-type: none"> <li>Interrupted time series with a control group</li> </ul>		randomised controlled trial		<ul style="list-style-type: none"> <li>Case-control study</li> </ul>
<b>III-3</b>	<p>A comparative study without concurrent controls:</p> <ul style="list-style-type: none"> <li>Historical control study</li> <li>Two or more single arm study</li> <li>Interrupted time series without a parallel control group</li> </ul>	Diagnostic case-control study	A retrospective cohort study	A case-control study	<p>A comparative study without concurrent controls:</p> <ul style="list-style-type: none"> <li>Historical control study</li> <li>Two or more single arm study</li> </ul>
<b>IV</b>	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. ([https://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/developers/nhmrc\\_levels\\_grades\\_evidence\\_120423.pdf](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf))

[Back to top](#)

## 2.7 References

1. ↑ <sup>1.0</sup> <sup>1.1</sup> National Health and Medical Research Council. *NHMRC levels of evidence and grades for recommendations for guideline developers*. Canberra: National Health and Medical Research Council; 2009 Available from: [https://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/developers/nhmrc\\_levels\\_grades\\_evidence\\_120423.pdf](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf).

[Back to top](#)

## 2.1 Complete lymph node dissection vs lymph node staging

### Contents

- 1 Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage I NSCLC?
  - 1.1 Introduction
  - 1.2 Complete lymph node dissection versus lymph node staging in stage I
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.1.1 Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage I NSCLC?

#### 2.1.1.1 Introduction

Mediastinal lymph node staging, either by pre-operative (mediastinoscopy, endobronchial ultrasound FNA) or intra-operative sampling is an integral part of surgical resection of NSCLC. Besides the prognostic value of proper staging, the current evidence base for adjuvant chemotherapy shows a survival advantage for patients receiving chemotherapy if any nodes are found to be positive. Whilst accurate lymph node staging should be standard practice, the evidence to date has been unclear as to when a complete mediastinal lymph node dissection is indicated, if at all.

[Back to top](#)

#### 2.1.1.2 Complete lymph node dissection versus lymph node staging in stage I

Despite a meta analysis demonstrating a survival benefit from mediastinal node dissection for all-comers having NSCLC resection<sup>[1]</sup>, the completion of a large randomised controlled trial by the American College of Surgeons Oncology Group<sup>[2]</sup>, confirmed that this benefit did not extend to patients who were staged intra-operatively with frozen section proven node negative disease. Another small trial of peripheral clinical stage I NSCLC less than 2cm in diameter also failed to demonstrate a benefit of complete mediastinal lymph node dissection<sup>[3]</sup>.

[Back to top](#)

## 2.1.2 Evidence summary and recommendations

Evidence summary	Level	References
Complete mediastinal lymph node dissection does not improve survival for patients having surgical resection for pathologically proven stage I NSCLC.	II	[2], [3]

Evidence-based recommendation	Grade
Mediastinal node dissection is recommended unless the patient has been staged intra-operatively as node negative by sampling and histological confirmation.	<b>B</b>

Practice point
For accurate staging according to AJCC TNM Pathological Staging, it is advisable to sample at least three lymph nodes from different stations. This is also required for prognostic purposes and for appropriate referral for adjuvant chemotherapy.

Back to top

## 2.1.3 References

1. ↑ Wright G, Manser RL, Byrnes G, Hart D, Campbell DA. *Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials*. Thorax 2006 Jul;61(7):597-603 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16449262>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> .
3. ↑ <sup>3.0</sup> <sup>3.1</sup> Sugi K, Nawata K, Fujita N, Ueda K, Tanaka T, Matsuoka T, et al. *Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter*. World J Surg 1998 Mar;22(3):290-4; discussion 294-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9494422>.

Back to top

## 2.1.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.2 Minimally invasive lobectomy vs open lobectomy

---

### **Contents**

- 1 Is minimally invasive lobectomy as effective as open lobectomy for treatment of operable stage I NSCLC?
  - 1.1 Introduction
- 2 Evidence summary and recommendations
  - 2.1 Long term survival after minimally invasive lobectomy for operable stage I NSCLC
- 3 References
- 4 Appendices



## 2.2.1 Is minimally invasive lobectomy as effective as open lobectomy for treatment of operable stage I NSCLC?

### 2.2.1.1 Introduction

Minimally invasive lobectomy is performed with the intention of achieving the same oncological outcomes as traditional lobectomy by thoracotomy, but with lesser impact in terms of pain, cosmesis, morbidity and post-operative recovery. The definition of minimally invasive lobectomy is somewhat broad, with variations in the size of the utility incision, use of rib-spreading, hilar dissection and node dissection. For the purpose of this guideline, minimally invasive (also known as Video-Assisted Thoracic Surgery, VATS or Thoracoscopic) lobectomy consists of a non-spreading utility incision, three to four instrument ports and dissection of individual hilar structures (viz. bronchus, artery, vein).

There has only been a single small pseudo-randomised controlled trial (randomised by ID number) showing equivalence in long term oncological outcomes with minimally invasive lobectomy<sup>[1]</sup>. The remaining long term survival evidence comes from systematic reviews of VATS lobectomy based on case-matched and propensity scored series. Relative risks for death within five years are either equivalent, or in the range of 0.45-0.97 with median relative risk in the range of 0.66-0.72 in favour of minimally invasive lobectomy<sup>[2][3][4][5]</sup>.

Evidence from a further small randomised controlled trial<sup>[6]</sup> and the above systematic reviews and propensity-scored analyses demonstrate a benefit for minimally invasive lobectomy with respect to overall complications and pulmonary complications. There appears to be a reduced risk of atrial fibrillation with minimally invasive lobectomy, but this evidence is derived only from propensity-scored and retrospective cohort studies.

[Back to top](#)

## 2.2.2 Evidence summary and recommendations

### 2.2.2.1 Long term survival after minimally invasive lobectomy for operable stage I NSCLC

Evidence summary	Level	References
Minimally invasive lobectomy is at least as effective as open lobectomy with respect to long term survival.	III-1, III-2	[1], [2], [3], [4], [5]
Minimally invasive lobectomy is at least as effective as open lobectomy with respect to reported post-operative complication rates.	II, III-2	[2], [4], [5], [6]

Evidence-based recommendation	Grade
Minimally invasive lobectomy is at least as effective as open lobectomy with respect to long term survival and reported post-operative complication rates.	<b>B</b>

[Back to top](#)

## 2.2.3 References

1. ↑ <sup>1.0 1.1</sup> Sugi K, Kaneda Y, Esato K. *Video-assisted thoracoscopic lobectomy achieves a satisfactory long-term prognosis in patients with clinical stage IA lung cancer*. World J Surg 2000 Jan;24(1):27-30; discussion 30-1 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10594199>.
2. ↑ <sup>2.0 2.1 2.2</sup> .
3. ↑ <sup>3.0 3.1</sup> Flores RM, Alam N. *Video-assisted thoracic surgery lobectomy (VATS), open thoracotomy, and the robot for lung cancer*. Ann Thorac Surg 2008 Feb;85(2):S710-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18222202>.
4. ↑ <sup>4.0 4.1 4.2</sup> .
5. ↑ <sup>5.0 5.1 5.2</sup> Yan TD, Black D, Bannon PG, McCaughan BC. *Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer*. J Clin Oncol 2009 May 20;27(15):2553-62 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19289625>.
6. ↑ <sup>6.0 6.1</sup> Kirby TJ, Mack MJ, Landreneau RJ, Rice TW. *Lobectomy--video-assisted thoracic surgery versus muscle-sparing thoracotomy. A randomized trial*. J Thorac Cardiovasc Surg 1995 May;109(5):997-1001; discussion 1001-2 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7739262>.

[Back to top](#)

## 2.2.4 Appendices

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.3 Radiotherapy

---

### Contents

- 1 What is the role of radiotherapy in the treatment of operable stage I NSCLC?
  - 1.1 Introduction
  - 1.2 Radiotherapy versus observation
  - 1.3 Surgery versus radiotherapy
  - 1.4 Surgery or radiotherapy for patients unsuitable for lobectomy
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.3.1 What is the role of radiotherapy in the treatment of operable stage I NSCLC?

---

#### 2.3.1.1 Introduction

Surgery, at least lobectomy, is the standard of care for patients with operable clinical stage I non-small cell lung cancer. Conventionally fractionated radiotherapy can be used in patients who refuse lobectomy.

Hypofractionated stereotactic ablative radiotherapy (SABR) is a new technique whose proponents argue that it may be as effective as lobectomy. In patients with poor lung function or other comorbidities who are judged high risk patients for lobectomy, limited surgery (segmentectomy or wedge resection) or radiotherapy, either conventional or SABR, may be options for curative treatment.

[Back to top](#)

#### 2.3.1.2 Radiotherapy versus observation

The evidence that radiotherapy (or surgery for that matter) alters the natural history of stage I NSCLC is indirect and largely derived from its effect on local control. In a non-randomised retrospective analysis of a patient registry, outcomes for 91 patients with operable and inoperable stage I NSCLC (pathologic confirmation not available in 17) were compared: survival was significantly longer in the radiotherapy group ( $P < 0.0001$ ). <sup>[1]</sup>

[Back to top](#)

### 2.3.1.3 Surgery versus radiotherapy

There has been no direct comparison of surgery with radiotherapy, either conventional or stereotactic ablative body radiotherapy (SABR), in patients with operable disease. Most studies compare patients having surgery with inoperable patients having radiotherapy, which introduces a bias favouring surgery. Surgically treated patients had superior survival even after adjusting for prognostic factors in an analysis of a population registry. <sup>[1]</sup>

A retrospective study comparing outcomes in patients having either lobectomy (n=149), wedge resection (n=47) or hyperfractionated accelerated radiotherapy (CHART) found improved survival in patients having surgery, but there were only 19 patients who had CHART. <sup>[2]</sup>

The survival of patients treated with lobectomy in a Spanish institution were compared with those of a group of patients treated by fractionated radiotherapy in the Netherlands. <sup>[3]</sup> The survival of the 110 surgical patients at three years was 78% and 44% in the radiotherapy group (P=0.0004). In 28 patient pairs matched by propensity scoring using age and FEV1, three year survival was 73% and 56% respectively (P=0.56).

In a single institution retrospective study, survival, local control and toxicity were compared in patients having resection versus SABR. <sup>[4]</sup> Most surgical patients had lobectomy, but other forms of resection were included. In the SABR group, only 80% had biopsy proven disease. After matching for age, stage and comorbidity in a subset of 114 patients, there were no differences in survival or local control. There were no treatment related deaths in the SABR group; in the matched surgical patients the operative mortality was 7%.

In a registry-based study limited to patients 75 or older, outcomes following resection or SABR were compared using a matched-pair analysis. At three years survival was 61% in the surgical group, and 47% in the SABR group (P=0.22). <sup>[5]</sup>

A systematic review of outcomes following surgery or SABR in patients with severe chronic obstructive pulmonary disease (COPD) (FEV1 < 50% predicted) concluded that survival was comparable with both forms of treatment, but three year survivals were highly variable ranging from 43 to 70%. <sup>[6]</sup>

[Back to top](#)

### 2.3.1.4 Surgery or radiotherapy for patients unsuitable for lobectomy

There has been no direct comparison of segmentectomy or wedge resection versus radiotherapy. There are three retrospective non-randomised single institution studies which have reported local control and survival following limited surgery or radiotherapy in patients unsuitable for lobectomy. In the first study, survival was better for patients having limited resection versus 3D conformal radiotherapy. <sup>[7]</sup> This difference was no longer evident after a multivariate analysis including other prognostic factors, or after a propensity-matched analysis.

In the second study the local control and survival at three years were 76% and 63% respectively for 40 patients having surgery, and 78% and 55% in 39 patients having conventionally fractionated radiotherapy. <sup>[8]</sup>

In the third study, the radiotherapy was given by a SABR technique.<sup>[9]</sup> Of the 55 radiotherapy patients, 52 were unfit for any surgery. There were 69 patients who underwent wedge resection. At 30 months, local recurrence had occurred in 20% of the surgical group and 4% of the radiotherapy patients ( $P=0.07$ ). Survival at 30 months was superior in patients having surgery compared with radiotherapy, possibly due to selection bias (87% vs 72%,  $P=0.01$ ).

Back to top

## 2.3.2 Evidence summary and recommendations

### Practice point

Radiotherapy is an alternative treatment option for patients who refuse surgery or are not fit for a standard lobectomy. There is insufficient evidence to recommend which method of radiotherapy (conventional or a hypofractionated stereotactic) is preferable.

Back to top

## 2.3.3 References

1. ↑ <sup>1.0</sup> <sup>1.1</sup> Birim O, Kappetein AP, Goorden T, van Klaveren RJ, Bogers AJ. *Proper treatment selection may improve survival in patients with clinical early-stage non-small cell lung cancer*. Ann Thorac Surg 2005 Sep; 80(3):1021-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16122477>.
2. ↑ Ghosh S, Sujendran V, Alexiou C, Beggs L, Beggs D. *Long term results of surgery versus continuous hyperfractionated accelerated radiotherapy (CHART) in patients aged >70 years with stage 1 non-small cell lung cancer*. Eur J Cardiothorac Surg 2003 Dec;24(6):1002-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14643820>.
3. ↑ Jimenez MF, van Baardwijk A, Aerts HJ, De Ruyscher D, Novoa NM, Varela G, et al. *Effectiveness of surgery and individualized high-dose hyperfractionated accelerated radiotherapy on survival in clinical stage I non-small cell lung cancer. A propensity score matched analysis*. Radiother Oncol 2010 Dec;97(3): 413-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20851487>.
4. ↑ Crabtree TD, Denlinger CE, Meyers BF, El Naqa I, Zoole J, Krupnick AS, et al. *Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer*. J Thorac Cardiovasc Surg 2010 Aug;140(2):377-86 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20400121>.
5. ↑ Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman B, Senan S. *Treatment of stage I NSCLC in elderly patients: A population-based matched-pair comparison of stereotactic radiotherapy versus surgery*. Radiother Oncol 2011 Jul 18 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21775007>.
6. ↑ Palma D, Lagerwaard F, Rodrigues G, Haasbeek C, Senan S. *Curative Treatment of Stage I Non-small-cell Lung Cancer in Patients with Severe COPD: Stereotactic Radiotherapy Outcomes and Systematic Review*. Int J Radiat Oncol Biol Phys 2011 Jun 1 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21640513>.

7. ↑ Yendamuri S, Komaki RR, Correa AM, Allen P, Wynn B, Blackmon S, et al. *Comparison of limited surgery and three-dimensional conformal radiation in high-risk patients with stage I non-small cell lung cancer.* J Thorac Oncol 2007 Nov;2(11):1022-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17975494>.
8. ↑ Hsie M, Morbidini-Gaffney S, Kohman LJ, Dexter E, Scalzetti EM, Bogart JA. *Definitive treatment of poor-risk patients with stage I lung cancer: a single institution experience.* J Thorac Oncol 2009 Jan;4(1):69-73 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19096309>.
9. ↑ .

[Back to top](#)

## 2.3.4 Appendices

---

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.4 Radiotherapy after surgery

---

### Contents

- 1 What is the role of radiotherapy after surgery in the treatment of operable stage I NSCLC?
  - 1.1 Introduction
  - 1.2 Postoperative external beam radiotherapy (PORT) versus no radiotherapy
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.4.1 What is the role of radiotherapy after surgery in the treatment of operable stage I NSCLC?

### 2.4.1.1 Introduction

Radiotherapy either to the tumour bed or the regional lymph nodes may be employed after surgery to reduce local recurrence, and possibly improve survival. The role of external beam radiotherapy following complete resection of NSCLC has been extensively investigated, but there is less information on the role of radiotherapy following incomplete removal of the tumour. In addition to external beam radiotherapy, brachytherapy using iodine-125 seeds applied to the tumour bed following sublobar resection has been investigated in a randomised trial<sup>[1]</sup> but until the results are released its use remains investigational.

[Back to top](#)

### 2.4.1.2 Postoperative external beam radiotherapy (PORT) versus no radiotherapy

There is strong evidence, based on an individual patient data meta-analysis and recently updated, that the use of postoperative radiotherapy following complete resection of stage I NSCLC is detrimental, and is associated with worse survival.<sup>[2]</sup>

In 665 patients with stage I disease randomised to PORT or no PORT, there was an increased risk of death with a hazard ratio of 1.42 (95% C.I.: 1.16, 1.75) in patients randomised to PORT.

[Back to top](#)

## 2.4.2 Evidence summary and recommendations

Evidence summary	Level	References
Following complete resection of stage I NSCLC, the addition of adjuvant external beam radiotherapy decreases survival.	I	[2]

Evidence-based recommendation	Grade
In patients who have had complete resection of stage I NSCLC, postoperative radiotherapy is not recommended.	<b>A</b>

### Practice point

In the absence of any evidence regarding the treatment of incompletely resected stage I disease unsuitable for further surgery, expert consensus opinion recommends that radiotherapy be given to the site of residual disease using the same dose and technique as if no resection had been performed.

[Back to top](#)

## 2.4.3 References

1. ↑ Fernando HC, Landreneau RJ, Mandrekar SJ, Hillman SL, Nichols FC, Meyers B, et al. *The impact of adjuvant brachytherapy with sublobar resection on pulmonary function and dyspnea in high-risk patients with operable disease: preliminary results from the American College of Surgeons Oncology Group Z4032 trial.* J Thorac Cardiovasc Surg 2011 Sep;142(3):554-62 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21724195>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> PORT Meta-analysis Trialists Group. *Postoperative radiotherapy for non-small cell lung cancer.* Cochrane Database Syst Rev 2005 Apr 18;(2):CD002142 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15846628>.

[Back to top](#)

## 2.4.4 Appendices

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.5 Chemotherapy before surgery



### Contents

- 1 What is the role of chemotherapy before surgery in the treatment of operable stage I NSCLC?
  - 1.1 Pre-operative neoadjuvant chemotherapy for stage IA
  - 1.2 Pre-operative neoadjuvant chemotherapy for stage IB
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.5.1 What is the role of chemotherapy before surgery in the treatment of operable stage I NSCLC?

### 2.5.1.1 Pre-operative neoadjuvant chemotherapy for stage IA

The pre-operative adjuvant therapy approach is predicated on clinical staging, which is principally based on radiological findings, rather than histological evaluation (aside from diagnostic biopsies). The majority of studies evaluating neoadjuvant (or pre-operative) chemotherapy for early stage NSCLC either excluded patients with clinical stage IA disease, or if included they represented a small percentage of the patients. Most studies do not segregate the stage I categories, and often pool stage I and II together in the study analyses. This makes subgroup evaluation of stage IA difficult or impossible. In studies where stage IA disease has been evaluated as a separate subgroup, the results have been variable. There is no confirmed survival benefit.

[Back to top](#)

### 2.5.1.2 Pre-operative neoadjuvant chemotherapy for stage IB

The benefit of chemotherapy before surgery is not well established in stage IB NSCLC. The French Thoracic Cooperative Group performed a trial of neoadjuvant cisplatin based chemotherapy in operable stage I,II and III NSCLC. A survival benefit was demonstrated in the pooled stage I and II subgroup.<sup>[1]</sup> One hundred and thirty one (131) of the total of 355 patients in this study had stage I disease. The Big Lung Trial (BLT/LU22) did not demonstrate a survival benefit for neoadjuvant chemotherapy in the overall study population, which included stage I, II and III NSCLC.<sup>[2]</sup> An associated systematic review did reveal a benefit.<sup>[3]</sup> A meta-analysis of 13 randomised controlled trials also showed a benefit, but this was particularly evident for patients with stage III NSCLC, whilst the findings for stage I and II were inconclusive.<sup>[4]</sup> A previous systematic review produced similar conclusions.<sup>[5]</sup> The Spanish Lung Cancer Group conducted a trial comparing surgery alone to neoadjuvant chemotherapy or post-operative chemotherapy (Carboplatin + Paclitaxel x three cycles). No benefit was seen with chemotherapy in stage I patients, regardless of whether the chemotherapy was administered before or after the surgery.<sup>[6]</sup> A meta-analysis comparing post-operative and pre-operative chemotherapy did not find a difference in outcome according to the timing of the chemotherapy around surgery.<sup>[7]</sup>

Brouchet et al<sup>[8]</sup> reported that pre-operative chemotherapy did not increase post-operative complications. In a phase II study from Japan, there were more complications post surgery if neoadjuvant chemotherapy is combined with radiotherapy and the dose of radiotherapy was greater than 45Gy.<sup>[9]</sup>

[Back to top](#)

## 2.5.2 Evidence summary and recommendations

Evidence summary	Level	References
There is insufficient data to support the use of chemotherapy before surgery for stage IA NSCLC.	I, II	[7], [6], [1]

Evidence-based recommendation	Grade
Neoadjuvant chemotherapy is not considered standard therapy for stage IA NSCLC.	<b>B</b>

Evidence summary	Level	References
There is insufficient data to support the administration of chemotherapy before surgery for stage IB NSCLC.	I, II	[7], [6], [1]

Evidence-based recommendation	Grade
Neoadjuvant chemotherapy is not considered standard therapy for stage IB NSCLC.	<b>B</b>

[Back to top](#)

## 2.5.3 References

1. ↑ 1.0 1.1 1.2 .
2. ↑ .
3. ↑ .
4. ↑ .

5. ↑ Burdett S, Stewart LA, Rydzewska L. *A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer*. J Thorac Oncol 2006 Sep;1(7):611-21 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17409927>.
6. ↑ <sup>6.0 6.1 6.2</sup> .
7. ↑ <sup>7.0 7.1 7.2</sup> Lim E, Harris G, Patel A, Adachi I, Edmonds L, Song F. *Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials*. J Thorac Oncol 2009 Nov;4(11):1380-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19861907>.
8. ↑ .
9. ↑ .

[Back to top](#)

## 2.5.4 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.6 Chemotherapy after surgery

---

### Contents

- 1 What is the role of chemotherapy after surgery in the treatment of operable stage I NSCLC?
  - 1.1 Post-operative adjuvant chemotherapy for stage IA
  - 1.2 Post-operative adjuvant chemotherapy for stage IB
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.6.1 What is the role of chemotherapy after surgery in the treatment of operable stage I NSCLC?

---

### 2.6.1.1 Post-operative adjuvant chemotherapy for stage IA

Trials of adjuvant chemotherapy in the form of the tablet Tegafur- Uracil have demonstrated a survival benefit, but these trials have involved Japanese patients only and the benefit has not been demonstrated for tumours less than 2 cm in size. Meta-analyses support this finding. One study, also from Japan, demonstrated a benefit with bestatin, an aminopeptidase inhibitor specifically for stage I NSCLC of squamous cell histology.<sup>[1]</sup> Chemotherapy has not been demonstrated to provide a benefit in this subgroup. In many studies, patients with stage IA are excluded. When included, stage IA patients usually represent a small percentage of the total patient numbers unless the study is specifically designed for stage I NSCLC only.

[Back to top](#)

### 2.6.1.2 Post-operative adjuvant chemotherapy for stage IB

As above, several trials from Japan have demonstrated a benefit for Tegafur- Uracil,<sup>[2][3]</sup> and another study from Japan showed a benefit with bestatin.<sup>[1]</sup> The role of chemotherapy, particularly platinum based combination chemotherapy, remains contentious in this setting. Pooled analyses of studies that investigated adjuvant chemotherapy using non-platinum based regimens, particularly alkylating agents, showed that patients treated with chemotherapy had worse survival. Adjuvant therapy utilizing platinum based chemotherapy combinations, however, has been associated with a survival advantage in the stage IB disease subgroup. Individual studies have produced variable results, but most of these have been inadequately powered to detect a survival advantage, accepting the better prognosis of this group and the small absolute benefit observed in several meta-analyses. The CALGB 9633 study specifically investigated stage IB NSCLC, and a survival benefit was not demonstrable. The study, however, was powered to detect a survival difference of 13% so smaller difference may have been missed. A subgroup analysis did suggest a benefit for patients with tumours that were greater than 4 cm in maximal diameter.<sup>[4]</sup> Two of the largest phase III trials that demonstrated a survival benefit used cisplatin combined with vinorelbine (JBR.10 (cisplatin + vinorelbine only) and ANITA (cisplatin + vinorelbine in 90% of patients). 45% of the patients from JBR.10 had stage IB disease and the remainder were stage II. The effect of chemotherapy appeared larger in patients with stage II disease, but the test for interaction was not significant and so the authors were reluctant to deduce that the effect of adjuvant chemotherapy is not seen in stage IB.<sup>[5]</sup> Longer term follow-up data from JBR.10 did reveal that there was a trend for interaction, suggesting that stage IB patients did not benefit.<sup>[6]</sup> A cost efficacy analysis from JBR.10 demonstrated that the cost of the benefit obtained was comparable to other accepted medical interventions. Compliance has also been shown to be high.<sup>[7]</sup> A Quality of Life analysis from JBR.10 did reveal maintenance of QoL for the majority of patients on adjuvant chemotherapy.<sup>[8]</sup> In the ANITA trial, 36% (301) of the patients had stage I. There was an absolute survival benefit of 8.6% at five years in the chemotherapy arm for all stages. The test for interaction between tumour stage and chemotherapy on survival was not significant, but there was a interaction trend (p=0.07) that suggested that patients with stage IB NSCLC did not benefit.<sup>[9]</sup>

A meta-analysis using individual patient data from four of the largest RCTs showed a benefit, but subgroup analysis again suggested the benefit was restricted to stage II and III.<sup>[10]</sup> The largest of the randomized controlled trials was the International Adjuvant Lung Cancer Trial, which included 681 patients with stage I disease. A survival benefit for chemotherapy with cisplatin containing regimens was seen. This benefit was not influenced by stage.<sup>[11]</sup> A small randomized phase II study from Italy did support a benefit in stage IB disease using cisplatin and etoposide.<sup>[12]</sup> An EORTC study showed no benefit for stage I-III NSCLC with adjuvant MVP – mitomycin, vinblastine and cisplatin.<sup>[13]</sup> Several meta-analyses and systematic reviews have demonstrated a survival benefit for stage IB disease, but of a small magnitude (less than 5%, usually 2-3%).

The Cochrane meta-analysis also addressed the question of the role of combined chemotherapy and radiotherapy given in the adjuvant setting. Four trials compared adjuvant chemo-radiation 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.

## 2.6.2 Evidence summary and recommendations

Evidence summary	Level	References
In studies of adjuvant chemotherapy for stage I NSCLC, stage IA patients were either excluded or represent a small percentage of the total number of included patients. There is no evidence of a clear survival benefit for post-operative adjuvant chemotherapy for stage IA disease.	II	[1], [2], [3], [4], [5], [6], [7], [8], [9], [11], [12], [13]

Evidence-based recommendation	Grade
Post-operative adjuvant chemotherapy is not recommended for stage IA NSCLC.	<b>B</b>

Evidence summary	Level	References
Platinum-based adjuvant chemotherapy for patients with stage IB NSCLC has not been consistently demonstrated to provide a survival benefit. Meta-analyses reveal a small absolute survival benefit, in the order of 2-3%. A subgroup analysis from one randomised trial suggested that there may be a benefit for tumours greater than 4 cm in maximal diameter.	II	[1], [2], [3], [4], [5], [6], [7], [8], [9], [11], [12], [13]

Evidence-based recommendation	Grade
Platinum-based adjuvant chemotherapy is not recommended for all patients with stage IB NSCLC.	<b>B</b>

### 2.6.3 References

1. ↑ 1.0 1.1 1.2 1.3 .
2. ↑ 2.0 2.1 2.2 Ueda H, Sakada T, Kuwahara M, Motohiro A. *A small randomized phase III single-center trial on postoperative UFT administration in patients with completely resected non-small cell lung cancer.* *Anticancer Drugs* 2004 Jan;15(1):29-33 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15090740>.
3. ↑ 3.0 3.1 3.2 .
4. ↑ 4.0 4.1 4.2 .
5. ↑ 5.0 5.1 5.2 .
6. ↑ 6.0 6.1 6.2 .
7. ↑ 7.0 7.1 7.2 .
8. ↑ 8.0 8.1 8.2 .
9. ↑ 9.0 9.1 9.2 .
10. ↑ .
11. ↑ 11.0 11.1 11.2 .
12. ↑ 12.0 12.1 12.2 .
13. ↑ 13.0 13.1 13.2 .

[Back to top](#)

### 2.6.4 Appendices

- [View recommendation components](#)
  - [View pending evidence](#)
  - [View body of evidence](#)
  - [View all comments](#)
  - [View literature search](#)
- [View PICO](#)

[Back to top](#)

## 2.7 Radiotherapy best practice

---

### Contents

- 1 What is the best practice radiotherapy approach in patients with stage I inoperable NSCLC?
  - 1.1 Introduction
  - 1.2 Optimal radiotherapy prescription for inoperable stage I NSCLC
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.7.1 What is the best practice radiotherapy approach in patients with stage I inoperable NSCLC?

---

#### 2.7.1.1 Introduction

In patients who have inoperable stage I non-small cell lung cancer, high dose radiotherapy is a curative treatment option.

There is indirect evidence, derived from the CHART randomised trial, that by improving local control, radiotherapy improves survival in inoperable NSCLC. The CHART trial compared hyperfractionated radiotherapy (three fractions per day to a total of 54 Gy) given over 12 days (CHART) with conventional radiotherapy given daily over six weeks to a total of 60 Gy in patients with inoperable NSCLC who had performance status of WHO 0 or 1.<sup>[1]</sup> The trial was open to patients with stages I-III; 30% were stage I. The trial demonstrated a survival advantage for patients randomised to CHART; there was no evidence that CHART was more or less effective according to stage. The survival benefit appeared to be in part a result of superior local control.

Other strategies to improve local control, and therefore survival, include concomitant chemotherapy and radiotherapy or dose escalation, either using conventional fractionation, or more recently with hypofractionated SABR. There are no studies directly comparing the effect of increased radiation dose, chemoradiation or hypofractionated SABR versus conventional dose/fractionation on survival specifically in stage I NSCLC. SABR is being used increasingly for the treatment of stage I NSCLC, based on a number of phase 2 studies reporting local control rates at two years in excess of 90% (e.g. Timmerman 2006, Timmerman 2010)<sup>[2][3]</sup>, but there are no studies demonstrating a survival advantage compared with conventional fractionation. Further, fatal toxicity

has been reported following SABR, particularly for centrally located tumours.<sup>[2]</sup> A systematic review of SABR concluded that there is a “need for more robust studies to define the optimum technical means of radiation delivery and dose fractionation parameters.”<sup>[4]</sup> The authors went on to say “Ideally, hypofractionated SBRT should be compared with surgery and best conventional radical radiotherapy using appropriate dose escalation.”

[Back to top](#)

### 2.7.1.2 Optimal radiotherapy prescription for inoperable stage I NSCLC

In the absence of comparative studies in populations with stage I NSCLC, recommendations for optimal dose and fractionation for this group of patients must rely to some extent on extrapolation of findings from trials conducted in populations with locally advanced disease alone or combined with patients with early stage disease. In this regard, the RTOG 73-01 trial which established 60 Gy in 30 fractions as the standard of care compared with lower doses for stage III disease has not been superseded.<sup>[5]</sup>

The CHART study compared a shortened 12 day treatment schedule to a total of 54 Gy (CHART) with conventional fractionation over 42 day to a total of 60 Gy.<sup>[1]</sup> The treatment was accelerated in the CHART arm by giving the radiotherapy three times per day. Patients randomised to CHART had longer survival with a 22% reduction in risk of death ( $P = 0.008$ ) and three year survival 20% vs 13%. The benefit appeared to be confined to patients with squamous cell carcinoma, but there was no difference in benefit according to stage. The CHARTWEL study compared a modification of CHART (no treatment on weekends) in which 60 Gy was given in 18 days compared with conventional fractionation, 66 Gy given in 6.5 weeks.<sup>[6]</sup> Ten percent of patients randomised had stage I disease. This study did not show a difference in survival between arms, either in the group as a whole, or within the stage I subset. Although shortening overall treatment time may improve local control and survival, the complexities of delivering treatment three times a day limit the applicability of the CHART findings in the Australian setting.

[Back to top](#)

### 2.7.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients with inoperable stage I NSCLC, improved local control following high dose radiotherapy is associated with a survival benefit.	II	[1]

Evidence-based recommendation	Grade
In patients with inoperable stage I NSCLC and good performance status, high dose radiotherapy is an appropriate treatment option.	<b>C</b>



Evidence summary	Level	References
A dose of 60 Gy in 30 fractions is associated with improved local control and survival compared with lower doses given by daily 2 Gy fractions.	II	[5]
Shortening overall radiotherapy treatment time may improve local control and survival.	II	[1], [6]

Evidence-based recommendation	Grade
In patients with inoperable stage I NSCLC, high dose radiotherapy to a total of 60 Gy in 30 fractions over six weeks is a reasonable option. CHART may be used as an alternative to radical conventionally fractionated RT, provided the appropriate resources are available.	<b>B</b>

Back to top

## 2.7.3 References

1. ↑ <sup>1.0 1.1 1.2 1.3</sup> Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. *Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee.* Radiother Oncol 1999 Aug;52(2):137-48 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10577699>.
2. ↑ <sup>2.0 2.1</sup> .
3. ↑ .
4. ↑ Brock J, Ashley S, Bedford J, Nioutsikou E, Partridge M, Brada M. *Review of hypofractionated small volume radiotherapy for early-stage non-small cell lung cancer.* Clin Oncol (R Coll Radiol) 2008 Nov;20(9):666-76 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18676130>.
5. ↑ <sup>5.0 5.1</sup> Perez CA, Bauer M, Edelstein S, Gillespie BW, Birch R. *Impact of tumor control on survival in carcinoma of the lung treated with irradiation.* Int J Radiat Oncol Biol Phys 1986 Apr;12(4):539-47 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3009368>.
6. ↑ <sup>6.0 6.1</sup> Baumann M, Herrmann T, Koch R, Matthiessen W, Appold S, Wahlers B, et al. *Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC).* Radiother Oncol 2011 Jul;100(1):76-85 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21757247>.

Back to top

## 2.7.4 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.8 Radiofrequency ablation

---

### Contents

- 1 What is the role of radiofrequency ablation in stage I inoperable NSCLC?
  - 1.1 Introduction
  - 1.2 Sublobar resection versus RFA
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.8.1 What is the role of radiofrequency ablation in stage I inoperable NSCLC?

---

#### 2.8.1.1 Introduction

Radiofrequency ablation (RFA) is a minimally invasive technique which uses a percutaneous probe to thermally ablate tumours of the liver and lung. It is a treatment option for patients who are unsuitable for lobectomy, which is the standard of care for stage I NSCLC.

[Back to top](#)

### 2.8.1.2 Sublobar resection versus RFA

One non-randomised single institution study compared outcomes following sublobar resection (n = 25), cryoablation therapy (n = 27) and RFA (n = 12) in 64 patients with stage I NSCLC judged unsuitable for lobectomy.<sup>[1]</sup> Survival at three years was in the range of 77 - 87% with no statistically significant differences between groups. Cancer free survival at three years was 61% for the sublobar resection group vs 50% for the RFA and 46% for the cryoablation groups (P > 0.05). There was a non-significant increase in incidence of pneumothorax and haemoptysis in the patients having non-surgical treatments. A second non-randomised single institution study compared sublobar resection (n = 45), 3D conformal radiotherapy (n = 39) and RFA (n = 12) in patients not fit for lobectomy, but no survival estimates were provided for the RFA group.<sup>[2]</sup> There were three cases of pneumothorax requiring therapy in patients having RFA, but none in the other groups.

[Back to top](#)

### 2.8.2 Evidence summary and recommendations

#### Practice point

Further studies are required to define the efficacy and toxicities of radiofrequency ablation in the treatment of stage I NSCLC before its routine use can be recommended.

#### Practice point

There are several techniques available for thermal ablation of tumours of which RFA is one. The others are microwave and cryo-ablation.

[Back to top](#)

### 2.8.3 References

1. ↑ Zemlyak A, Moore WH, Bilfinger TV. *Comparison of survival after sublobar resections and ablative therapies for stage I non-small cell lung cancer*. J Am Coll Surg 2010 Jul;211(1):68-72 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20610251>.
2. ↑ Hsie M, Morbidini-Gaffney S, Kohman LJ, Dexter E, Scalzetti EM, Bogart JA. *Definitive treatment of poor-risk patients with stage I lung cancer: a single institution experience*. J Thorac Oncol 2009 Jan;4(1):69-73 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19096309>.

[Back to top](#)

## 2.8.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.9 Radiotherapy plus chemotherapy

---

### **Contents**

- 1 What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage I NSCLC?
  - 1.1 The addition of chemotherapy to radiotherapy in inoperable stage I NSCLC
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.9.1 What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage I NSCLC?

### 2.9.1.1 The addition of chemotherapy to radiotherapy in inoperable stage I NSCLC

Patients with stage I disease are usually operable, but surgery may not be possible due to comorbidity, poor lung function, tumour location or patient choice. In those patients the traditional treatment approach has comprised of radiotherapy alone, usually given over five or six weeks with curative intent.<sup>[1]</sup> Studies have consistently demonstrated a survival benefit when chemotherapy is combined with such radiotherapy in inoperable NSCLC, but these studies were restricted to stage III non-small cell lung cancer.<sup>[2][3]</sup> We do not have evidence that demonstrates the same benefit in inoperable stage I disease as this question has never been evaluated in a randomised clinical trial for this early stage of lung cancer.

[Back to top](#)

## 2.9.2 Evidence summary and recommendations

### Practice point

Insufficient evidence exists to recommend routine use of chemotherapy along with radiation for the treatment of patients with inoperable stage I NSCLC.

[Back to top](#)

## 2.9.3 References

1. ↑ Rowell NP, Williams CJ. *Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable)*. Cochrane Database Syst Rev 2001;(1): CD002935 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11279780>.
2. ↑ Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. *Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410*. J Natl Cancer Inst 2011 Oct 5;103(19):1452-60 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21903745>.
3. ↑ Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. *Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer*. J Clin Oncol 1999 Sep;17(9):2692-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10561343>.

[Back to top](#)

## 2.9.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.10 Complete lymph node dissection vs lymph node staging

---

### **Contents**

- 1 Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage II NSCLC?
  - 1.1 Introduction
  - 1.2 Complete lymph node dissection versus lymph node staging in stage II
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.10.1 Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage II NSCLC?

### 2.10.1.1 Introduction

This evidence relates to patients who have had standard therapy with at least lobectomy and lymph node sampling. Mediastinal lymph node staging, either by pre-operative (mediastinoscopy, endobronchial ultrasound FNA) or intra-operative sampling is an integral part of surgical resection of NSCLC. Besides the prognostic value of proper staging, the current evidence base for adjuvant chemotherapy shows a survival advantage for patients receiving chemotherapy if any nodes are found to be positive.

[Back to top](#)

### 2.10.1.2 Complete lymph node dissection versus lymph node staging in stage II

Whilst accurate lymph node staging should be standard practice, the evidence to date has been unclear as to when a complete mediastinal lymph node dissection is indicated, if at all. In a Cochrane review by Manser et al<sup>[1]</sup>, it was found that the evidence already existed for a survival benefit from complete mediastinal lymph node dissection. This was specifically reported in 2006<sup>[2]</sup>, but did not generate the level of interest that accompanies new pharmacological interventions. The randomised trials by Wu et al<sup>[3]</sup> and Passlick et al<sup>[4]</sup> showed an increasing benefit for higher stage disease, but the Will Rogers phenomenon of stage migration could not be ruled out as a source of bias. It was not until the publication of the American College of Surgeons Oncology Group Z30 trial<sup>[5]</sup>, that it could be inferred that the benefit of complete mediastinal dissection is clearest in stage II and higher NSCLC.

[Back to top](#)

## 2.10.2 Evidence summary and recommendations

Evidence summary	Level	References
Complete mediastinal lymph node dissection is associated with improved overall survival compared to lymph node staging alone in patients with unknown stage or stage II-III NSCLC.	I, II	[1], [4], [2], [3]

Evidence-based recommendation	Grade
A complete mediastinal lymph node dissection of at least Stations 2R, 4R, 7 and 8 (right side) or Stations 5, 6, 7 and 8 (left side) is recommended for surgically resected stage II NSCLC.	<b>B</b>

[Back to top](#)

### 2.10.3 References

---

1. ↑ <sup>1.0 1.1</sup> Manser R, Wright G, Hart D, Byrnes G, Campbell DA. *Surgery for early stage non-small cell lung cancer*. Cochrane Database Syst Rev 2005 Jan 25;(1):CD004699 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15674959>.
2. ↑ <sup>2.0 2.1</sup> Wright G, Manser RL, Byrnes G, Hart D, Campbell DA. *Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials*. Thorax 2006 Jul;61(7):597-603 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16449262>.
3. ↑ <sup>3.0 3.1</sup> Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. *A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer*. Lung Cancer 2002 Apr;36(1):1-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11891025>.
4. ↑ <sup>4.0 4.1</sup> Passlick B, Kubuschock B, Siene W, Thetter O, Pantel K, Izbicki JR. *Mediastinal lymphadenectomy in non-small cell lung cancer: effectiveness in patients with or without nodal micrometastases - results of a preliminary study*. Eur J Cardiothorac Surg 2002 Mar;21(3):520-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11888774>.
5. ↑ .

[Back to top](#)

### 2.10.4 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.11 Radiotherapy after surgery

---



### Contents

- 1 What is the role of radiotherapy after surgery in the treatment of operable stage II NSCLC?
  - 1.1 Introduction
  - 1.2 Postoperative external beam radiotherapy (PORT) versus no radiotherapy
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.11.1 What is the role of radiotherapy after surgery in the treatment of operable stage II NSCLC?

### 2.11.1.1 Introduction

Radiotherapy either to the tumour bed or to the regional lymph nodes may be employed after surgery to reduce local recurrence, and possibly improve survival. The role of external beam radiotherapy following complete resection of NSCLC has been extensively investigated, but there is less information on the role of radiotherapy following incomplete removal of the tumour.

[Back to top](#)

### 2.11.1.2 Postoperative external beam radiotherapy (PORT) versus no radiotherapy

There is strong evidence, based on an individual patient data meta-analysis and recently updated, that the use of postoperative radiotherapy following complete resection of stage II NSCLC is detrimental, and is associated with worse survival. <sup>[1]</sup>

In 718 patients with stage II disease randomised to PORT or no PORT, there was an increased risk of death with a hazard ratio was 1.24 (95% C.I.: 1.04, 1.52) in patients randomised to PORT.

[Back to top](#)

## 2.11.2 Evidence summary and recommendations

Evidence summary	Level	References
Following complete resection of stage II NSCLC, the addition of adjuvant external beam radiotherapy decreases survival	I	[1]

Evidence-based recommendation	Grade
In patients who have had complete resection of stage II NSCLC, postoperative radiotherapy is not recommended.	<b>A</b>

[Back to top](#)

### 2.11.3 References

1. ↑ <sup>1.0</sup> <sup>1.1</sup> PORT Meta-analysis Trialists Group. *Postoperative radiotherapy for non-small cell lung cancer*. Cochrane Database Syst Rev 2005 Apr 18;(2):CD002142 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15846628>.

[Back to top](#)

### 2.11.4 Appendices

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.12 Chemotherapy before surgery

## Contents

- 1 What is the role of chemotherapy before surgery in the treatment of operable stage II NSCLC?
  - 1.1 Introduction
  - 1.2 Neoadjuvant chemotherapy
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.12.1 What is the role of chemotherapy before surgery in the treatment of operable stage II NSCLC?

### 2.12.1.1 Introduction

This clinical practice guideline addresses the question of the role of chemotherapy before surgery or neoadjuvant chemotherapy in operable stage II lung cancer. This does not address treatment of tumours involving superior sulcus. There are theoretical advantages in using chemotherapy in this setting, although available evidence is non-conclusive. Randomised controlled trials (RCTs) and meta-analysis have been confounded by low number of patients with stage II disease, poor accrual, early closure and significant heterogeneity. Sub group analysis of these trials cannot be considered as conclusive evidence regarding use of neoadjuvant chemotherapy.

[Back to top](#)

### 2.12.1.2 Neoadjuvant chemotherapy

The major evidence on which these guidelines are based comes from five RCTs and two meta-analyses. The salient features of the RCTs are depicted in the Table - Summary of five randomised trials comparing neoadjuvant chemotherapy with surgery alone.

The recently published CHEST trial<sup>[1]</sup> had progression free survival (PFS) as its primary end point. The HR for PFS and overall survival (OS) was significant in favour of the neoadjuvant chemotherapy arm. Patients with stage IIB/IIIA were grouped together and showed significant benefit for both PFS and OS compared to control group while IB/IIA patients did not have any significant benefit. This contrasts with results of the S9900 trial,<sup>[2]</sup> which did not show any significant OS difference in the overall population, while subgroup IB/IIA demonstrated a significant OS benefit. The NATCH trial<sup>[3]</sup> had an adjuvant arm in addition to the neoadjuvant chemotherapy arm. The primary endpoint of this study was disease free survival (DFS). There was no difference in DFS and OS amongst the three groups. Stage II patients receiving neoadjuvant chemotherapy demonstrated a trend towards improved DFS, which failed to reach statistical significance. Interestingly 90% of subjects in the neoadjuvant chemotherapy arm completed all planned chemotherapy compared with 60% in the postoperative arm. Surgical outcomes and postoperative mortality were similar. The European intergroup trial MRC-LU22 EORTC NVALT trial<sup>[4]</sup> did not demonstrate any overall survival benefit with neoadjuvant chemotherapy. Neoadjuvant

chemotherapy did not have any impact on the quality of life. The FTCS study<sup>[5]</sup> did not demonstrate any survival benefit in the population studied. However, subset analysis revealed survival benefit in stage I/II disease. The compliance rates were very good across the trials, ranging from 75-90%. The response rates ranged from 34% to 64%. A systematic review and meta-analysis<sup>[6]</sup> including 988 patients across seven RCTs demonstrated an overall survival benefit (HR 0.82, 95% CI 0.69-0.97; P=0.02). This equated to an absolute improvement in overall survival of 7% at five years in patients with stage II disease. Updated analysis including the LU22 trial<sup>[4]</sup> demonstrated a shift in HR to 0.88 (0.76-1.01) with the benefits not maintaining statistical significance. However, these meta-analyses were not based in individual patient data and meaningful subgroup analysis could not be undertaken for early stage disease due to significant heterogeneity amongst the trials. The benefits of neoadjuvant chemotherapy are similar to that of adjuvant chemotherapy with absolute benefit of 6% at five years from meta-analysis.<sup>[6]</sup> However, the overall evidence is insufficient to recommend neoadjuvant chemotherapy as standard therapy for operable stage II NSCLC. Individual patient meta-analysis of all the available trials may help to clarify this question further across all the sub-groups.

[Back to top](#)

## 2.12.2 Evidence summary and recommendations

Evidence summary	Level	References
The evidence of benefit for neoadjuvant chemotherapy in stage II disease is unclear with trials having inconsistent end points and lacking power due to poor accrual and early closure.	II	[3], [2], [1]
Majority of individual trials do not show statistically significant benefit in stage II disease.	II	[5], [3], [4], [2]
Neoadjuvant chemotherapy does not adversely affect the quality of life.	II	[4]
Compliance to neoadjuvant chemotherapy is better compared to adjuvant chemotherapy.	II	[3]
Meta-analysis showed overall survival benefit, however subset analysis for stage II disease was not undertaken due to heterogeneity of individual trials included.	I	[6]
The benefits of neoadjuvant chemotherapy are similar to that of adjuvant chemotherapy	I	[6], [7]

Evidence-based recommendation	Grade
Chemotherapy before surgery is not recommended as standard of care for patients with operable stage II NSCLC.	<b>B</b>

Evidence-based recommendation	Grade
Chemotherapy before surgery in operable stage II disease, with at least three cycles of platinum-based regimes, may be considered in select patients, who are unlikely to receive it as adjuvant therapy.	<b>C</b>

[Back to top](#)

### 2.12.3 References

1. ↑ <sup>1.0 1.1</sup> Scagliotti GV, Pastorino U, Vansteenkiste JF, Spaggiari L, Facciolo F, Orlovski TM, et al. *Randomized Phase III Study of Surgery Alone or Surgery Plus Preoperative Cisplatin and Gemcitabine in Stages IB to IIIA Non-Small-Cell Lung Cancer*. J Clin Oncol 2012 Jan 10;30(2):172-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22124104>.
2. ↑ <sup>2.0 2.1 2.2</sup> .
3. ↑ <sup>3.0 3.1 3.2 3.3</sup> .
4. ↑ <sup>4.0 4.1 4.2 4.3</sup> .
5. ↑ <sup>5.0 5.1</sup> .
6. ↑ <sup>6.0 6.1 6.2 6.3</sup> Burdett S, Stewart LA, Rydzewska L. *A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer*. J Thorac Oncol 2006 Sep;1(7):611-21 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17409927>.
7. ↑ Non-small Cell Lung Cancer Collaborative Group. *Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials*. BMJ 1995;311(7010): 899-909 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7580546>.

[Back to top](#)

### 2.12.4 Appendices

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.13 Chemotherapy after surgery

### Contents

- 1 What is the role of chemotherapy after surgery in the treatment of operable stage II NSCLC?
  - 1.1 Introduction
  - 1.2 Chemotherapy after surgery in stage II NSCLC
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.13.1 What is the role of chemotherapy after surgery in the treatment of operable stage II NSCLC?

#### 2.13.1.1 Introduction

This clinical practice guideline addresses the question of the role of chemotherapy after complete resection of stage II NSCLC. The primary outcome assessed while preparing these guidelines is overall survival. The studies examined have used the 6th edition of TNM staging. Curative treatment for early stage NSCLC is surgery.

However 30-60% of patients treated with surgery develops recurrence.<sup>[1][2][3]</sup> Many of the recurrences are systemic, indicating that adjuvant treatment might be beneficial. The question of adjuvant treatment in patients with positive margins after surgery has not been addressed here. Adjuvant use of Tegafur- Uracil is excluded as these drugs have not been well studied in Caucasian population.

[Back to top](#)

#### 2.13.1.2 Chemotherapy after surgery in stage II NSCLC

Several studies have confirmed the benefit of adjuvant chemotherapy in Stage II NSCLC. A large meta-analysis of individual patient data<sup>[4]</sup> involving 8447 patients from 34 trials (1291 stage II patients) reported a 5% (from 40 to 45%) absolute benefit in overall survival, at five years, in stage II patients, using platinum based chemotherapy. These results are confirmed by results of a pooled analysis (LACE meta-analysis) of individual patient data from five well designed, large, randomised controlled trials which included a total of 4584 patients.

Out of this 1616 patients had stage II disease.<sup>[5]</sup> At a median follow up of 5.1 years the absolute overall survival benefit was 5.4% for the whole population and 10% for stage II patients (from 39% to 49%) with HR of death for stage II patients at 0.83 (95% CI 0.73-0.95). This analysis included only patients treated with Cisplatin based chemotherapy as this was shown to be the combination most effective in a previous large meta-analysis. The same study also revealed combination of alkylating agents with Cisplatin to be detrimental and this combination is no longer recommended.<sup>[6]</sup>

The major characteristics of the five major randomised controlled trials, included in the LACE meta-analysis mentioned above, are shown in Table - Summary of five randomised trials included in the LACE meta-analysis. These constitute the major evidence on which these guidelines are based upon. The first three trials showed a survival benefit with adjuvant Cisplatin based chemotherapy while the last two did not. The Big lung trial was underpowered to demonstrate survival benefit. The IALT is the largest trial and was the first RCT to demonstrate a statistically significant benefit in overall survival.<sup>[7]</sup> However, in an updated publication, with a median follow up of 7.5 years, the survival benefit in favour of chemotherapy became non-significant.<sup>[8]</sup> In contrast, results of long term follow up of the JBR 10 trial (median 9.3 years), showed that the survival benefits continued to be significant for the overall population as well as for patients with stage II disease.<sup>[9][10]</sup> The median age was similar in all the trials. The majority of patients had good performance status (ECOG 0, 1) with only 4.5-7.2% of patients having an ECOG performance status of 2, in trials including them. At least 50% of enrolled patients completed the planned number of chemotherapy cycles across the studies. The dose of Cisplatin varied from 80-120mg/m<sup>2</sup> per cycle. Cisplatin was combined with Vinorelbine in two of the trials while in the rest, it was combined with a range of other drugs. These include Etoposide, other Vinca alkaloids, Mitomycin C, Ifosfamide and Prednisolone.

Pre-specified subset analysis of the LACE meta-analysis looking at the combination of Cisplatin and Vinorelbine found this combination to be superior in terms of overall survival when compared to the other combinations. HR 0.80, 95% CI: 0.70-0.91, p<0.001 versus HR 0.95, 95% CI: 0.86- 1.05, p = 0.33.<sup>[11]</sup> Chemotherapy was reasonably well tolerated with 50% or more patients completing all planned cycles. Toxic deaths reported ranged from 0.8 % (JBR 10) to 2% (IALT).<sup>[12]</sup> The absolute survival benefit at five years in the three positive trials ranged from 3.9 % (IALT), 8.6% (ANITA) and 15% (JBR10). Quality of life (QOL) of the patients were reported from the JBR10 trial. It was seen that the QOL was impaired in the immediate period following chemotherapy. However, scores improved to match the control group within a period of nine months. QOL scores for peripheral neuropathy and hearing impairment persisted in the chemotherapy group for up to 30 months.<sup>[13]</sup>

The Cancer and Leukemia Group B trial (CALGB 9633) looked at benefit of four cycles of Paclitaxel/Carboplatin as adjuvant treatment in patients with stage IB NSCLC. The regime was well tolerated with no toxic deaths. The trial did not demonstrate any overall survival benefit. However, in an exploratory subset analysis of the trial, patients with tumour diameter >4cm demonstrated a significant survival advantage.<sup>[14]</sup> These tumours would be classified under IIA in the 7th edition of TNM classification. However, no firm recommendation can be made regarding adjuvant chemotherapy in this subgroup.

[Back to top](#)

## 2.13.2 Evidence summary and recommendations

---

Evidence summary	Level	References
In patients with operable stage II NSCLC, the evidence supports the use of 3-4 cycles of adjuvant cisplatin based chemotherapy.	I, II	[11], [6], [15], [5], [7], [8], [10], [12], [16], [9], [17]

Evidence-based recommendation	Grade
Patients with completely resected stage II NSCLC should be offered 3-4 cycles of adjuvant cisplatin based chemotherapy.	<b>A</b>

Practice point
<p>The chemotherapy combination of cisplatin and vinorelbine was the most widely studied regimen which showed benefit.</p> <p>There is insufficient evidence to support adjuvant chemotherapy for patients with ECOG performance status of <math>\geq 2</math>.</p> <p>No recommendation can be made for patients who have had less than a lobectomy.</p> <p>Based on the 7th edition of TNM classification tumour size of <math>&gt;5\text{cm}</math> would fall under stage IIA. These patients may be considered for adjuvant chemotherapy.</p>

Back to top

### 2.13.3 References

1. ↑ Ponn RB, Lo Cicero J III, Rusch VW. *BDT: Surgical treatment of non-small cell lung cancer*. In: Shields TW, Lo Cicero J III, Ponn R, Rusch VW, editors. General Thoracic surgery. 6th ed. Philadelphia: Lippincott Williams & Wilkins 2005;p.1548-1587.
2. ↑ Mountain CF. *Revisions in the International System for Staging Lung Cancer*. Chest 1997 Jun;111(6): 1710-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9187198>.
3. ↑ Rosell R, Felip E, Maestre J, Sanchez JM, Sanchez JJ, Manzano JL, et al. *The role of chemotherapy in early non-small-cell lung cancer management*. Lung Cancer 2001 Dec;34 Suppl 3:S63-74 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11740997>.
4. ↑ Non-Small Cell Lung Cancer Collaborative Group. *Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer*. Cochrane Database Syst Rev 2010 May 12;(5): CD007309 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20464750>.
5. ↑ <sup>5.0</sup> 5.1 .



6. ↑ <sup>6.0</sup> <sup>6.1</sup> Non-small Cell Lung Cancer Collaborative Group. *Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials*. *BMJ* 1995;311 (7010):899-909 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7580546>.
7. ↑ <sup>7.0</sup> <sup>7.1</sup> .
8. ↑ <sup>8.0</sup> <sup>8.1</sup> .
9. ↑ <sup>9.0</sup> <sup>9.1</sup> .
10. ↑ <sup>10.0</sup> <sup>10.1</sup> .
11. ↑ <sup>11.0</sup> <sup>11.1</sup> .
12. ↑ <sup>12.0</sup> <sup>12.1</sup> .
13. ↑ .
14. ↑ .
15. ↑ .
16. ↑ .
17. ↑ .

[Back to top](#)

## 2.13.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.14 Radiotherapy best practice

---

### Contents

1 What is the best practice radiotherapy approach in patients with stage II inoperable NSCLC?

2 Evidence summary and recommendations  
3 References  
4 Appendices

## 2.14.1 What is the best practice radiotherapy approach in patients with stage II inoperable NSCLC?

As in stage I NSCLC, surgery is the standard of care for patients with stage II NSCLC. In patients who are not fit for surgery, radiotherapy may be a curative option.

Stage II disease constitutes a small proportion of all patients with NSCLC, therefore, it is unusual to find studies restricted to this population of patients. In the CHART study, 7% of patients had stage II disease;<sup>[1]</sup> in the CHARTWEL study, it was 6%.<sup>[2]</sup> Because of the paucity of evidence for inoperable stage II disease, it seems reasonable to use the recommendation guidelines for stage III disease, to which the reader is directed, (refer radiotherapy stage III inoperable).

## 2.14.2 Evidence summary and recommendations

### Practice point

Patients with inoperable stage II disease could be offered radiotherapy with curative intent.

Back to top

## 2.14.3 References

1. ↑ Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. *Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee.* Radiother Oncol 1999 Aug;52(2): 137-48 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10577699>.
2. ↑ Baumann M, Herrmann T, Koch R, Matthiessen W, Appold S, Wahlers B, et al. *Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC).* Radiother Oncol 2011 Jul; 100(1):76-85 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21757247>.

Back to top

## 2.14.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.15 Radiotherapy plus chemotherapy

---

### **Contents**

- 1 What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage II NSCLC?
  - 1.1 Introduction
  - 1.2 Radiation alone versus combination chemo-radiotherapy
  - 1.3 Concurrent versus sequential therapy
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.15.1 What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage II NSCLC?

---

### 2.15.1.1 Introduction

Curative intent radiotherapy is a treatment option, however, there is scarce data available regarding the use of both chemotherapy and radiotherapy in the management of inoperable stage II NSCLC. Studies looking at concurrent and/or sequential chemotherapy and radiotherapy mainly include patients with stage III disease. Extrapolation of these data to stage II patients should be interpreted with caution.

[Back to top](#)

### 2.15.1.2 Radiation alone versus combination chemo-radiotherapy

In an individual patient meta-analysis of 1764 patients, comparing concomitant chemo-radiotherapy with radiation alone,<sup>[1]</sup> concomitant platin-based chemo-radiation was shown to improve survival for locally advanced NSCLC. Hazard ratio of death was 0.89(95%CI, 0.81-0.98; p=0.02). This corresponds to an absolute benefit of 4% at two years and 2.2% at five years. Toxicity data was not available in this analysis. However, the study mainly consisted of patients with stage III disease with stage II patients constituting only 2% of the total number of patients in each arm.

The Cochrane meta-analysis<sup>[2]</sup> showed that chemo-radiotherapy significantly reduced overall risk of death (HR 0.71, 95%CI 0.64 to 0.80; 1607 participants) and overall progression free survival at any site (HR 0.69, 95% CI 0.58 to 0.81; I2 45%; 1145 participants). Incidence of acute oesophagitis, neutropenia and anaemia were significantly increased with concurrent chemo-radiation. However the number of patients with stage II disease was small to make any definite conclusion for this group.

[Back to top](#)

### 2.15.1.3 Concurrent versus sequential therapy

In a meta-analysis of concomitant versus sequential radio-chemotherapy,<sup>[3]</sup> 1205 patients from six trials were included. With a median follow up of six years there was a significant benefit on overall survival for concomitant radio-chemotherapy (HR 0.84; 92%CI, 0.74-0.95; p=0.004). Concomitant therapy also improved loco-regional control (HR 0.77; 95% CI, 0.62-0.95; p=0.01). There was no effect on distant metastasis. Concomitant therapy was also associated with increased risk of acute Oesophagitis, however, there was no significant acute pulmonary toxicity. This analysis also mainly consisted of patients with stage III disease with very few patients (12) with stage II disease.

[Back to top](#)

## 2.15.2 Evidence summary and recommendations

Evidence summary	Level	References
There is insufficient evidence to support the use of chemotherapy along with radiation, given either concomitantly or sequentially, in the treatment of inoperable stage II disease.	I	[1], [3], [2]

Evidence-based recommendation	Grade
Insufficient evidence exists to recommend routine use of chemotherapy along with radiation for the treatment of patients with inoperable stage II NSCLC.	<b>C</b>

Practice point
Patients with inoperable stage II disease could be offered radiotherapy with curative intent. Patients with good performance status and organ function may be considered for definitive concurrent chemo-radiation with a platin-based regime. This has to be balanced with an increased risk of toxicity. This is based on data extrapolated from studies mainly including inoperable stage III disease.

Back to top

## 2.15.3 References

1. ↑ <sup>1.0 1.1</sup> Aupérin A, Le Péchoux C, Pignon JP, Koning C, Jeremic B, Clamon G, et al. *Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients*. Ann Oncol 2006 Mar;17(3):473-83 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16500915>.
2. ↑ <sup>2.0 2.1</sup> O'Rourke N, Roqué I Figuls M, Farré Bernadó N, Macbeth F. *Concurrent chemoradiotherapy in non-small cell lung cancer*. Cochrane Database Syst Rev 2010 Jun 16;(6):CD002140 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20556756>.
3. ↑ <sup>3.0 3.1</sup> .

Back to top

## 2.15.4 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.16 Radiotherapy after surgery

---

### Contents

- 1 What is the role of postoperative radiotherapy (PORT) in resected stage III NSCLC?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Post-operative Radiotherapy
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

### 2.16.1 What is the role of postoperative radiotherapy (PORT) in resected stage III NSCLC?

---

#### 2.16.1.1 Introduction

Despite gross complete surgical resection of NSCLC, the incidence of local/regional failure is significant. Retrospective and prospective studies, performed in

the pre-adjuvant chemotherapy era, report crude local-regional failure rates of 6%-28% for N0 disease, 18% to 49% for N1 disease, and 6% to 65% for N2 disease.

<sup>[1]</sup> The use of adjuvant chemotherapy following the resection of stage II-IIIa NSCLC is associated with a survival advantage and is now considered the standard of care.<sup>[2]</sup> However, the effect of adjuvant chemotherapy on loco-regional control is not clear.

[Back to top](#)

### 2.16.2.1 Post-operative Radiotherapy

The use of radiotherapy (RT) post surgical resection reduces the risk of local recurrence.<sup>[3][4][5][6]</sup> The effect of PORT on survival, particularly in patients with pN2 disease, is controversial.

A meta-analysis of 11 randomised controlled trials involving 2343 patients undergoing complete resection of stage I-III disease randomised to PORT or observation demonstrated a significant adverse effect of PORT on survival (hazard ratio 1.18, 95% CI 1.07-1.31,  $p=0.001$ ) corresponding to an absolute detriment in survival of 5% at two years (95% CI 2%-9%).<sup>[7]</sup> In exploratory subgroup analyses the most pronounced survival detriment was observed in patients with stage I/II and N0-N1 disease. In patients with stage III, N2 disease, there was no clear evidence of an adverse or beneficial effect of PORT on survival.

The applicability of these results to current day practice is questionable because the treatments utilised in the included studies (particularly the radiation dose, field size and mode of delivery) differ substantially from those available currently.

Data from two more recent non-randomised studies suggest a benefit for PORT in pN2 disease, and confirm a detrimental effect for PORT in pN0 and pN1 disease.

A retrospective study using the Surveillance, Epidemiology and End Results (SEER) database identified 7,465 patients who underwent surgery for stage II or III NSCLC between 1988 and 2002, 47% of whom subsequently received PORT.<sup>[8]</sup> It was presumed that given the time period involved, modern radiotherapy techniques were employed although no details of treatment technique were provided. The use of PORT did not have a significant impact on survival. However, in subset analysis the use of PORT was associated with a significant increase in survival (HR 0.855; 95% CI 0.762-0.959,  $p=.0077$ ) for patients with N2 nodal disease. PORT was associated with a significant decrease in survival for patients with N0 (HR 1.176; 95%CI 1.005-1.376,  $p=.0435$ ) and N1 (HR 1.097, 95% CI 1.015 to 1.186) nodal disease. It must be remembered that the use of PORT was not randomised in this analysis.

In the Adjuvant Navelbine International Trialist Association (ANITA) trial, patients with pN0-pN2 disease were randomised to receive postoperative chemotherapy or observation.<sup>[9]</sup> Administration of PORT was recommended for patients with pathological node-positive disease, but patients were not randomised to PORT and it was not mandatory. The recommended regimen was 45 -60Gy over five weeks using a high-energy linear accelerator with treatment initiated two weeks after the completion of chemotherapy or within two weeks of randomised in the observation group. Overall 27.6% of patients received PORT, of whom 50% had pN2 disease.

### 2.16.2 Defining operable and inoperable disease in stage III

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**[Read full explanation](#)**

A hypothesis-generating sub-analysis of this trial found higher five-year overall survivals in those patients with pN2 disease who received PORT, in both the observation and chemotherapy arms (21% versus 17% and 47% versus 34%, respectively; statistical tests of comparison not conducted). For patients with pN1 disease, those who were assigned to no chemotherapy and received PORT had a better survival than those who did not (median survival 50 versus 26m) but in those who received chemotherapy, the use of PORT was associated with a survival detriment (median survival 47 versus 94m). It must be remembered that local-regional failure was not the primary endpoint of this study and PORT was not randomly assigned.

These results suggesting a potential benefit for PORT in pN2 disease need to be clarified in prospective randomised trials. Unfortunately, a trial conducted by the Cancer and Leukemia Group (CALGB 9734) in which patients with completely resected stage IIIA (N2) disease received four cycles of adjuvant paclitaxel/carboplatin and were then randomised to adjuvant RT or observation, closed early due to poor accrual.<sup>[10]</sup>

The Lung Adjuvant Radiotherapy Trial (LUNG ART) is currently recruiting patients in Europe. In this Phase III trial patients with completely resected III-N2 disease are randomised between PORT and no PORT, irrespective of chemotherapy use.<sup>[11]</sup>

Positive Margins: There is a paucity of data regarding the use of PORT for positive surgical margins. Drawing on experience from the use of RT in other tumour sites, the use of PORT in this setting may be considered.<sup>[12]</sup>

[Back to top](#)

### 2.16.3 Evidence summary and recommendations

Evidence summary	Level	References
A meta-analysis demonstrates no clear evidence of an adverse or beneficial effect of PORT on survival in patients with pN2 disease. The applicability of this finding to current day practice is questionable.	I	[7]
Data from two more recent but non-randomised studies suggest a survival benefit for PORT in pN2 disease.	II, III-2	[8], [9]

Evidence-based recommendation	Grade
Post-operative radiation therapy in patients with pN2 disease is not recommended for routine use because of the lack of prospective randomised clinical trial data demonstrating an improvement in survival. The use of PORT could be considered in selected patients with pN2 disease.	<b>C</b>



### Practice point

Post-operative radiation therapy may be considered in the setting of a positive margin.

[Back to top](#)

## 2.16.4 References

1. ↑ Kelsey CR, Marks LB, Hollis D, Hubbs JL, Ready NE, D'Amico TA, et al. *Local recurrence after surgery for early stage lung cancer: an 11-year experience with 975 patients*. *Cancer* 2009 Nov 15;115(22):5218-27 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19672942>.
2. ↑ .
3. ↑ Lung Cancer Study Group.. *Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid carcinoma of the lung*. *N Engl J Med* 1986;315: 1377-1382. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2877397>.
4. ↑ Stephens RJ, Girling DJ, Bleehen NM, Moghissi K, Yosef HM, Machin D. *The role of post-operative radiotherapy in non-small-cell lung cancer: a multicentre randomised trial in patients with pathologically staged T1-2, N1-2, M0 disease*. *Medical Research Council Lung Cancer Working Party*. *Br J Cancer* 1996 Aug;74(4):632-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8761382>.
5. ↑ Mayer R, Smolle-Juettner FM, Szolar D, Stuecklschweiger GF, Quehenberger F, Friehs G, et al. *Postoperative radiotherapy in radically resected non-small cell lung cancer*. *Chest* 1997 Oct;112(4):954-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9377958>.
6. ↑ Van Houtte P, Rocmans P, Smets P, Goffin JC, Lustman-Maréchal J, Vanderhoeft P, et al. *Postoperative radiation therapy in lung cancer: a controlled trial after resection of curative design*. *Int J Radiat Oncol Biol Phys* 1980 Aug;6(8):983-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6998936>.
7. ↑ <sup>7.0</sup> <sup>7.1</sup> PORT Meta-analysis Trialists Group. *Postoperative radiotherapy for non-small cell lung cancer*. *Cochrane Database Syst Rev* 2005 Apr 18;(2):CD002142 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15846628>.
8. ↑ <sup>8.0</sup> <sup>8.1</sup> Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. *Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database*. *J Clin Oncol* 2006 Jul 1;24(19):2998-3006 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16769986>.
9. ↑ <sup>9.0</sup> <sup>9.1</sup> .
10. ↑ .
11. ↑ .
12. ↑ Saynak M, Higginson DS, Morris DE, Marks LB. *Current status of postoperative radiation for non-small-cell lung cancer*. *Semin Radiat Oncol* 2010 Jul;20(3):192-200 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20685582>.

[Back to top](#)

## 2.16.5 Appendices

---

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.17 Mediastinal lymph node dissection

---

### Contents

- 1 What is the clinical benefit of mediastinal lymph node dissection in stage IIIA operable NSCLC?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Complete lymph node dissection versus lymph node staging in stage IIIA
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

### 2.17.1 What is the clinical benefit of mediastinal lymph node dissection in stage IIIA operable NSCLC?

---

#### 2.17.1.1 Introduction

This evidence relates to patients who have had standard therapy with at least lobectomy and lymph node sampling. Mediastinal lymph node staging, either

by pre-operative (mediastinoscopy, endobronchial ultrasound FNA) or intra-operative sampling is an integral part of surgical resection of NSCLC. Besides the prognostic value of proper staging, the current evidence base for adjuvant chemotherapy shows a survival advantage for patients receiving chemotherapy if any nodes are found to be positive.

## 2.17.2 Defining operable and inoperable disease in stage III

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**Read full explanation**

### 2.17.2.1 Complete lymph node dissection versus lymph node staging in stage IIIA

Whilst accurate lymph node staging should be standard practice, the evidence to date has been unclear as to when a complete mediastinal lymph node dissection is indicated, if at all. In a Cochrane review by Manser et al<sup>[1]</sup>, it was found that the evidence already existed for a survival benefit from complete mediastinal lymph node dissection. This was specifically reported in 2006<sup>[2]</sup>, but did not generate the level of interest that accompanies new pharmacological interventions. The randomised trials by Wu et al<sup>[3]</sup> and Passlick et al<sup>[4]</sup> showed an increasing benefit for higher stage disease, but the Will Rogers phenomenon of stage migration could not be ruled out as a source of bias. It was not until the publication of the American College of Surgeons Oncology Group Z30 trial<sup>[5]</sup>, that it could be inferred that the benefit of complete mediastinal dissection is clearest in stage II and higher NSCLC.

[Back to top](#)

### 2.17.3 Evidence summary and recommendations

Evidence summary	Level	References
Complete mediastinal lymph node dissection is associated with improved overall survival compared to lymph node staging alone in patients with unknown stage or stage II-IIIa surgically resected NSCLC.	I, II	[1], [2], [6], [3], [4]

Evidence-based recommendation	Grade
A complete mediastinal lymph node dissection of at least Stations 2R, 4R, 7 and 8 (right side) or Stations 5, 6, 7 and 8 (left side) is recommended for surgically resected stage IIIA NSCLC.	<b>B</b>

[Back to top](#)

## 2.17.4 References

---

1. ↑ <sup>1.0</sup> <sup>1.1</sup> Manser R, Wright G, Hart D, Byrnes G, Campbell DA. *Surgery for early stage non-small cell lung cancer*. Cochrane Database Syst Rev 2005 Jan 25;(1):CD004699 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15674959>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> Wright G, Manser RL, Byrnes G, Hart D, Campbell DA. *Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials*. Thorax 2006 Jul;61(7):597-603 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16449262>.
3. ↑ <sup>3.0</sup> <sup>3.1</sup> Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. *A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer*. Lung Cancer 2002 Apr;36(1):1-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11891025>.
4. ↑ <sup>4.0</sup> <sup>4.1</sup> Passlick B, Kubuschock B, Siene W, Thetter O, Pantel K, Izbicki JR. *Mediastinal lymphadenectomy in non-small cell lung cancer: effectiveness in patients with or without nodal micrometastases - results of a preliminary study*. Eur J Cardiothorac Surg 2002 Mar;21(3):520-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11888774>.
5. ↑ .
6. ↑ Hughes MJ, Chowdhry MF, Woolley SM, Walker WS. *In patients undergoing lung resection for non-small cell lung cancer, is lymph node dissection or sampling superior?* Interact Cardiovasc Thorac Surg 2011 Sep;13(3):311-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21606053>.

[Back to top](#)

## 2.17.5 Appendices

---

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.18 Surgery after chemoradiotherapy

---

### Contents

- 1 What is the clinical benefit of the addition of surgery to definitive chemoradiotherapy in stage IIIA (N2) NSCLC?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Induction chemoradiotherapy and surgery: Randomised controlled trials
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

## 2.18.1 What is the clinical benefit of the addition of surgery to definitive chemoradiotherapy in stage IIIA (N2) NSCLC?

### 2.18.1.1 Introduction

Definitive chemoradiotherapy (CRT) is a standard of care in clinical N2 NSCLC.<sup>[1][2][3]</sup> Theoretical improvements in local control with the addition of surgery must be balanced against the increased morbidity and mortality of surgery.

[Back to top](#)

### 2.18.2 Defining operable and inoperable disease in stage III

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**[Read full explanation](#)**

#### 2.18.2.1 Induction chemoradiotherapy and surgery: Randomised controlled trials

Albain et al (RTOG 93-09 / Int 139)<sup>[4]</sup> randomised 396 patients with operable T1-3, biopsy proven N2, M0 NSCLC to concurrent chemotherapy (cisplatin and etoposide) and daily radiotherapy (45 Gy) followed in the absence of progression by either surgical resection or continued radiotherapy (16 Gy). Both groups received two cycles of consolidative chemotherapy. Patients had baseline FEV1 > 2L or PPO FEV1 > 800 ml on quantitative V/Q, good performance status and less than 10% weight loss with in the previous three months.

The trial was well powered (93%) to detect a 10% difference in the primary end point of overall survival and analysed on an intention to treat basis. There was no significant difference in overall survival between the two treatment groups (HR = 0.87, 95% CI: 0.69 - 1.10 [P = 0.24]). Progression-free survival was improved in the surgical arm (HR = 0.77, 95% CI: 0.62 - 0.96 [P = 0.017]). At 5 years, 22% of participants in the CRT/surgery arm were disease-free compared with 11% of participants in the CRT arm.

Eight percent of participants died from treatment related causes in the CRT/surgery group compared with 2% in the CRT group. The majority of treatment-related deaths in the surgical group occurred after pneumonectomy (14 out of 16), with only one death occurring after lobectomy. Post hoc subgroup analysis suggested there may be an improvement in overall survival in those who are judged to be suitable for lobectomy at the outset of treatment.

[Back to top](#)

### 2.18.3 Evidence summary and recommendations

Evidence summary	Level	References
CRT (45 Gy) followed by surgery compared to definitive CRT (61 Gy) in unselected patients with cIIIA (N2) NSCLC does not result in improved overall survival.	II	[4]
CRT (45 Gy) followed by surgery compared to definitive CRT (61 Gy) in unselected patients with cIIIA (N2) NSCLC results in improved progression free survival.	II	[4]

Evidence-based recommendation	Grade
Unselected patients with biopsy confirmed stage IIIA (N2) disease are best treated with chemoradiotherapy alone.	<b>B</b>

Practice point
Induction chemoradiotherapy followed by surgery in selected patients with cIIIA (N2) disease is feasible and improves progression-free survival. Provided the patient does not require a pneumonectomy, the addition of surgery may improve overall survival.

[Back to top](#)

## 2.18.4 References

---

1. ↑ National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) Dermatofibrosarcoma Protuberans Version 1.2012*. 2011 Sep 27 Available from: [http://www.nccn.org/professionals/physician\\_gls/pdf/dfsp.pdf](http://www.nccn.org/professionals/physician_gls/pdf/dfsp.pdf).
2. ↑ Robinson LA, Ruckdeschel JC, Wagner H Jr, Stevens CW, American College of Chest Physicians. *Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition)*. *Chest* 2007 Sep;132(3 Suppl):243S-265S Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17873172>.
3. ↑ Australian Cancer Network Management of Lung Cancer Guidelines Working Party. *Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Lung Cancer*. The Cancer Council Australia and Australian Cancer Network, National Health and Medical Research Council Canberra 2004.
4. ↑ 4.0 4.1 4.2 .

[Back to top](#)

## 2.18.5 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.19 Adjuvant chemotherapy

---

### Contents

- 1 What is the clinical benefit of adjuvant chemotherapy for patients with stage III operable NSCLC?
  - 1.1 Introduction

2	Defining operable and inoperable disease in stage III
2.1	Surgery and adjuvant chemotherapy versus surgery alone
3	Evidence summary and recommendations
4	References
5	Appendices

## 2.19.1 What is the clinical benefit of adjuvant chemotherapy for patients with stage III operable NSCLC?

### 2.19.1.1 Introduction

Operable stage III non-small cell lung cancer (NSCLC) has a poor prognosis although considerable heterogeneity in the T and N classifications of stage III disease results in variable five year survival rates e.g. 15-35% and 5-10% for stages IIIA and IIIB disease, respectively.<sup>[1]</sup> Operability may be determined on medical or surgical grounds or for reasons of patient preference. The true extent of heterogeneity of stage IIIA disease can further refined by sub-classifying N2 involvement.<sup>[2]</sup> Stage IIIB NSCLC with N3 disease is considered inoperable although surgery may be indicated for carefully selected patients with T4N0-1M0 disease.<sup>[3]</sup> The prognosis of stage III NSCLC is poor because the risk of death originates from either locoregional recurrence or distant recurrence. Therefore, treatment strategies in operable stage III disease have been designed to counter both types of relapse. In addition to radiotherapy, chemotherapy may be given preoperatively as neoadjuvant or primary chemotherapy or postoperatively as adjuvant chemotherapy, or as both.

As has been shown convincingly for breast and colorectal cancers, the overall rationale for post-operative chemotherapy for resectable or resected node-positive NSCLC is the delivery of a systemic modality of anti-cancer treatment that may reduce risk of death from micrometastatic disease. Nonetheless, cytotoxic chemotherapy is a significant cause of morbidity and mortality that may militate against its beneficial effects.

The rationale for adjuvant chemotherapy is accurate knowledge of pathological stage and prognosis, and its major disadvantage is the lower rate of delivery in the post-operative setting.

[Back to top](#)

### 2.19.2 Defining operable and inoperable disease in stage III

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

#### **Read full explanation**



### 2.19.2.1 Surgery and adjuvant chemotherapy versus surgery alone

The 1995 Non-Small Cell Lung Cancer Collaborative Group meta-analysis based on individual patient data<sup>[4]</sup> indicated that cisplatin-based chemotherapy after surgery might increase survival (hazard ratio [HR] 0.87, 95% CI 0.74 - 1.02;  $p=0.08$ ), and was equivalent to an absolute benefit of 5% at five years. This study sparked a number of randomised controlled clinical trials designed to provide a definitive answer to the question of the role of adjuvant chemotherapy in resected NSCLC. The results of these studies have been inconsistent leading to the conduct of two independent meta-analyses based on individual patient data.<sup>[5][6]</sup>

In the meta-analyses from the NSCLC Collaborative Group, an absolute improvement in five-year survival of 5% (95% CI, 3-8) for stage III disease (from 30% to 35%) was observed. In all but one trial (CALGB 9633), cisplatin was the platinum agent. Also in this group, although there was no evidence of difference in the effect of chemotherapy between patients with good and poor performance status, an increasing relative effect of chemotherapy with improving performance status (PS) (trend  $p=0.002$ ) was noted and was consistent across trials.<sup>[6]</sup>

In the LACE meta-analysis<sup>[5]</sup>, a 17% reduction in risk of death for stage III NSCLC patients was identified. The HR for patients with stage III disease was 0.83 (95% CI, 0.72 - 0.94). Chemotherapy was likely to be detrimental for patients with PS of 2. A small excess of non-lung cancer deaths was observed in the adjuvant chemotherapy group in the first six months, which corresponded to a 2% decrease in survival with chemotherapy from 98.6% to 96.6%. The non-lung cancer deaths were mainly related to chemotherapy toxicity and an excess of pulmonary/cardiovascular deaths. Significantly more elderly patients ( $\geq 70$  years) died from non-lung cancer-related causes, and elderly patients received significantly lower first and total cisplatin doses, and fewer chemotherapy cycles.<sup>[7]</sup>

A subgroup analysis for the cisplatin-vinorelbine regimen had been pre-specified in the LACE statistical analysis plan. Patients who were randomised to cisplatin-vinorelbine or observation were the largest subgroup (41%) and were the most homogeneous in terms of drug doses and eligibility. There was a significant interaction of cisplatin-vinorelbine effect and stage III disease. The greatest benefit was seen in patients with stage III disease who had a 14.7% improvement in overall survival at five years. In comparison with untreated controls, the HR of overall survival for adjuvant cisplatin/vinorelbine chemotherapy in patients with stage III disease was 0.66 (95% CI, 0.53 - 0.83).<sup>[8]</sup> There is a suggestion that higher exposure to cisplatin (cumulative dose  $>300\text{mg/m}^2$ ) may confer a greater benefit although in the group of patients receiving cisplatin-vinorelbine, this effect cannot be dissociated from any benefit that may be conferred by the companion drug(s).

Adjuvant chemotherapy is not without toxicity. Chemotherapy-related deaths were 0.9% in the LACE meta-analysis<sup>[5]</sup> and 1.4% for patients receiving cisplatin-vinorelbine versus 0.4% for those patients receiving cisplatin in combination with other drugs<sup>[8]</sup>.

Interestingly, longer term follow up of IALT<sup>[9]</sup>, which was the largest study in the LACE meta-analysis, showed continued benefit of adjuvant chemotherapy but which was no longer statistically significant. Although the survival benefit continued to be manifest as reduced recurrence rates at local and distant sites (with the exception of brain), its extent may have been diminished by accumulating non-lung cancer deaths more than five years post-randomisation. The statistically significant causes of non-cancer deaths were infections and circulatory and respiratory diseases rather than second cancers.<sup>[9]</sup>

In the North American intergroup 0160/Southwest Oncology Group (SWOG) 9416, 111 patients with T3-T4 N0-N1 tumours were treated with preoperative cisplatin and etoposide and concurrent radiation to 45Gy in 25 fractions. Following restaging at two to four weeks, patients with stable or responsive disease underwent thoracotomy. All patients were to receive an additional two cycles of chemotherapy. With this approach 75% (83 of 111) patients completed the entire treatment regimen. A complete resection (R0) was possible in 75 patients (90%) and gross total resection (R0 or R1) in 76 patients (92%). A five-year survival of 44% was reported for the entire group and for cases in which a complete response was achieved, the five-year survival was 54%. The authors reported these results were achieved with acceptable morbidity and mortality. The mortality rate was 2.7%. There was no information on quality of life.<sup>[10]</sup>

[Back to top](#)

### 2.19.3 Evidence summary and recommendations

Evidence summary	Level	References
In patients with completely resected stage III NSCLC, adjuvant cisplatin-based chemotherapy increases survival compared with observation. Further research is required to identify which stage III patients have the most favourable risk-benefit profile for adjuvant chemotherapy.	I	[6], [5]
The extent of this survival benefit diminishes with time as the number of non-lung cancer deaths accumulates.	I	[5]

Evidence-based recommendation	Grade
Patients who have a good performance status (WHO 1, 2) and completely resected stage III non-small cell lung cancer should be offered adjuvant cisplatin-based chemotherapy.	<b>A</b>

Evidence summary	Level	References
Limited evidence from one well-conducted study supports using induction chemoradiotherapy for locoregional control for patients with superior sulcus NSCLC.	III-3	[10]

Evidence-based recommendation	Grade
Patients with superior sulcus NSCLC may be considered for induction chemoradiotherapy.	<b>C</b>

Practice point
Caution is advised in recommending adjuvant cisplatin-based chemotherapy to good performance status patients who are 70 years of age or older and/or who have clinically significant cardio-respiratory or renal co-morbidities.

Back to top

## 2.19.4 References

1. ↑ Burdett SS, Stewart LA, Rydzewska L. *Chemotherapy and surgery versus surgery alone in non-small cell lung cancer*. Cochrane Database Syst Rev 2007 Jul 18;(3):CD006157 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17636828>.
2. ↑ Ruckdeschel JC. *Combined modality therapy of non-small cell lung cancer*. Semin Oncol 1997 Aug;24(4): 429-39 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9280223>.
3. ↑ Jett JR, Schild SE, Keith RL, Kesler KA, American College of Chest Physicians. *Treatment of non-small cell lung cancer, stage IIIB: ACCP evidence-based clinical practice guidelines (2nd edition)*. Chest 2007 Sep; 132(3 Suppl):266S-276S Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17873173>.
4. ↑ Non-small Cell Lung Cancer Collaborative Group. *Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials*. BMJ 1995;311(7010): 899-909 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7580546>.
5. ↑ 5.0 5.1 5.2 5.3 5.4 .
6. ↑ 6.0 6.1 6.2 .
7. ↑ Früh M, Rolland E, Pignon JP, Seymour L, Ding K, Tribodet H, et al. *Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer*. J Clin Oncol 2008 Jul 20;26(21):3573-81 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18640938>.
8. ↑ 8.0 8.1 .
9. ↑ 9.0 9.1 .
10. ↑ 10.0 10.1 .

Back to top

## 2.19.5 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.20 Neoadjuvant chemotherapy

---

### Contents

- 1 What is the clinical benefit of neoadjuvant chemotherapy for patients with stage III operable NSCLC?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Neoadjuvant chemotherapy and surgery versus surgery alone
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

### 2.20.1 What is the clinical benefit of neoadjuvant chemotherapy for patients with stage III operable NSCLC?

---

#### 2.20.1.1 Introduction

The clinical rationale for neoadjuvant chemotherapy includes:

- (i) availability of clinical and/or pathological assessment of treatment response to indicate the likelihood of systemic disease control
- (ii) tumour regression to improve the chances of successful tumour resection, and
- (iii) increased chemotherapy delivery rate as chemotherapy would be better tolerated before rather than after major surgery.

Conversely, major disadvantages of neoadjuvant chemotherapy are

- (i) chemotherapy-induced accelerated tumour cell repopulation, and
- (ii) delay in performing a potentially curative operation thus risking metastatic spread if the chemotherapy is ineffective.

[Back to top](#)

### 2.20.2.1 Neoadjuvant chemotherapy and surgery versus surgery alone

Reliable evidence is not yet available to show a consistently beneficial survival effect of neoadjuvant chemotherapy in stage III NSCLC. A systematic review and literature-based meta-analysis was unable to establish if stage III NSCLC patients benefited from neoadjuvant chemotherapy.<sup>[1]</sup> An indirect comparison meta-analysis was performed to obtain the relative hazards on survival of postoperative to preoperative chemotherapy administration in patients with resectable NSCLC.<sup>[2]</sup> Stage III patients were not analysed separately and in the final analysis, there were no evident differences in overall and disease-free survival in the timing of chemotherapy administration.<sup>[2]</sup> A subgroup meta-analysis was performed within a literature-based meta-analysis to understand the possible survival benefits of neoadjuvant chemotherapy in stage III NSCLC patients.<sup>[3]</sup> The quality of evidence in this study was low with a substantial risk of bias. Furthermore, in the absence of a meta-analysis based on individual patient data, the clinical significance of finding a combined HR of neoadjuvant chemotherapy in stage III NSCLC patients of 0.84 (95% CI, 0.75 - 0.95; p=0.005) is uncertain.

[Back to top](#)

### 2.20.3 Evidence summary and recommendations

Evidence summary	Level	References
Neoadjuvant platinum-based chemotherapy confers an overall survival benefit. However, the extent of this benefit in patients with stage III disease is less well defined. An individual patient-based meta-analysis is awaited and may better define the survival benefit of neoadjuvant chemotherapy in stage III patients.	I	[1], [2], [3]

### 2.20.2 Defining operable and inoperable disease in stage III

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**Read full explanation**

Evidence-based recommendation	Grade
The quality of the evidence and the size of the effect are not sufficient to recommend routine application of neoadjuvant platinum-based chemotherapy in the treatment of patients with stage III non-small cell lung cancer.	<b>C</b>

Practice point
Stage III non-small cell lung cancer patients being considered for neoadjuvant chemotherapy can be reviewed in a lung cancer-specific multidisciplinary meeting.

Back to top

## 2.20.4 References

1. ↑ <sup>1.0 1.1</sup> Burdett SS, Stewart LA, Rydzewska L. *Chemotherapy and surgery versus surgery alone in non-small cell lung cancer*. Cochrane Database Syst Rev 2007 Jul 18;(3):CD006157 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17636828>.
2. ↑ <sup>2.0 2.1 2.2</sup> Lim E, Harris G, Patel A, Adachi I, Edmonds L, Song F. *Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials*. J Thorac Oncol 2009 Nov;4(11):1380-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19861907>.
3. ↑ <sup>3.0 3.1</sup> .

Back to top

## 2.20.5 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.21 Neoadjuvant radiotherapy plus neoadjuvant chemotherapy

---

### **Contents**

- 1 What is the clinical benefit of the addition of neoadjuvant radiotherapy to neoadjuvant chemotherapy in stage IIIA (N2) NSCLC?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Randomised controlled trials of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

### 2.21.1 What is the clinical benefit of the addition of neoadjuvant radiotherapy to neoadjuvant chemotherapy in stage IIIA (N2) NSCLC?

---

#### 2.21.1.1 Introduction

Neoadjuvant chemotherapy followed by surgical resection became a standard of care internationally in clinical N2 NSCLC<sup>[1][2][3]</sup> based on the very poor survival of patients treated with surgery alone in this setting.<sup>[4][5][6][7]</sup> Theoretical improvements in resectability, local control and subsequent survival with the addition of radiotherapy to neoadjuvant chemotherapy must be balanced against the potentially increased morbidity and mortality of surgery in this setting.

[Back to top](#)

### 2.21.2.1 Randomised controlled trials of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy

Girard et al (IFCT - 0101)<sup>[8]</sup> randomised 46 patients with resectable cIIIA-N2 NSCLC in a phase II study with primary endpoint of feasibility. Response rate was significantly higher after neoadjuvant chemoradiotherapy versus chemotherapy alone (87% versus 57%,  $p = 0.049$ ).

Despite two completed phase 3 studies published only in abstract form<sup>[9][10]</sup> and a third well designed trial attempted by the RTOG and abandoned due to poor accrual<sup>[11]</sup> only one phase 3 study (enrolling a majority of cIIIB patients) has ever been published.

Thomas et al<sup>[12][13]</sup> randomised 558 patients with cIII (67% cIIIB) NSCLC between 1995 and 2003 at multiple German institutions, to:

1. three cycles of cisplatin and etoposide, followed by
2. twice-daily RT [45Gy] with concurrent carboplatin and vindesine, and then
3. surgical resection (and further RT [24Gy] if less than R0 resection)

versus

1. three cycles of cisplatin and etoposide, followed by
2. surgery, and
3. adjuvant radiotherapy (54Gy and further 24Gy if less than R0 resection).

On an intention to treat basis 37% versus 32% (NS) achieved complete resection. In those undergoing resection, complete resection was more often possible in the intervention group (75% versus 60% [ $p=0.008$ ]). In patients with complete resection, mediastinal downstaging (46% versus 29% [ $p=0.02$ ]) and pathological response (60% versus 20% [ $p<0.0001$ ]) favoured the preoperative chemoradiation group.

Despite this evidence of improved loco-regional response, there was no difference in PFS (primary endpoint). Of interest, post operative mortality favoured the control group (5% versus 9% [ $p=0.11$ ]), the trend being stronger after pneumonectomy (6% versus 14% [NS]), which was required in 35% in both arms.

[Back to top](#)

### 2.21.2 Defining operable and inoperable disease in stage III

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**Read full explanation**



### 2.21.3 Evidence summary and recommendations

Evidence summary	Level	References
Neoadjuvant chemotherapy, with or without radiotherapy, is feasible.	III-1, II	[8], [12], [13]
In patients with stage cIIIA (N2) NSCLC planned for surgery, preoperative chemoradiation compared to preoperative chemotherapy alone increases pathological response and mediastinal downstaging.	III-1, II	[8], [12], [13]
In unselected patients with stage cIIIA (N2) NSCLC planned for surgery, preoperative chemoradiation compared to preoperative chemotherapy alone has not been shown to improve PFS or OS.	III-1, II	[8], [12], [13]

Evidence-based recommendation	Grade
In selected patients (excellent performance status and cardio respiratory reserve) with stage cIIIA (N2) NSCLC, planned for surgery that will entail less than pneumonectomy, it is reasonable to offer neoadjuvant chemoradiotherapy.	<b>C</b>

Practice point
Surgery alone is not advised in cIIIA (N2) disease.

Back to top

### 2.21.4 References

1. ↑ Scottish Intercollegiate Guidelines Network. *Sign 80: Management of patients with lung cancer. A national clinical guideline*. Edinburgh: Scottish Intercollegiate Guidelines Network; 2005 Available from: <http://www.sign.ac.uk/guidelines/fulltext/80/index.html>.
2. ↑ National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer*. NCCN 2011;Version 3 Available from: [http://www.nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf).

3. ↑ Australian Cancer Network Management of Lung Cancer Guidelines Working Party. *Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Lung Cancer*. The Cancer Council Australia and Australian Cancer Network, National Health and Medical Research Council Canberra 2004.
4. ↑ Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB Jr, Lee JS, et al. *A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer*. J Natl Cancer Inst 1994 May 4;86(9):673-80 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8158698>.
5. ↑ Roth JA, Atkinson EN, Fossella F, Komaki R, Bernadette Ryan M, Putnam JB Jr, et al. *Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer*. Lung Cancer 1998 Jul;21(1):1-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9792048>.
6. ↑ Rosell R, Gómez-Codina J, Camps C, Maestre J, Padille J, Cantó A, et al. *A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer*. N Engl J Med 1994 Jan 20;330(3):153-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8043059>.
7. ↑ Rosell R, Gómez-Codina J, Camps C, Javier Sánchez J, Maestre J, Padilla J, et al. *Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial*. Lung Cancer 1999 Oct;26(1):7-14 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10574676>.
8. ↑ 8.0 8.1 8.2 8.3 .
9. ↑ Tada H, Tanaka M, Katakami N, Kurata T, Mitsudomi T, Negoro S, Kudoh S, Nishiyama H, Nishimura Y, and Nakagawa K. *Phase III study of induction chemotherapy (docetaxel and carboplatin) with or without radiotherapy followed by surgery in patients with stage IIIA (pN2) non-small cell lung cancer (NSCLC): WJTOG9903*. Journal of Clinical Oncology 2009;27:15 SUPPL. 1 (7556) Available from: <http://www.embase.com.ezproxy1.library.usyd.edu.au/search/results?subaction=viewrecord&rid=2&page=1&L70242257>.
10. ↑ Fleck J, Camargo J, Godoy D, Teixeira P, Graga-Filho A, Barletta A. *Chemoradiation therapy alone versus chemotherapy alone as a neoadjuvant treatment for stage III non-small-cell lung cancer. Preliminary report of a phase III, randomized trial*. Proc Am Soc Clin Oncol 1993;11:1108.
11. ↑ Radiation Therapy Oncology Group. *RTOG 0412 Protocol Information (updated 2011 August 4; cited 2012 April 4)*. 2012 Available from: <http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0412>.
12. ↑ 12.0 12.1 12.2 12.3 .
13. ↑ 13.0 13.1 13.2 13.3 .

Back to top

## 2.21.5 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.22 Recommended treatment approach

---

### **Contents**

- 1 What is the recommended treatment approach for the definitive management of patients with good performance status and inoperable stage III disease?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Surgery in inoperable N2 disease
  - 2.2 Radiation therapy
  - 2.3 Chemotherapy and radiation therapy
    - 2.3.1 Radiation alone versus combination chemoradiotherapy
    - 2.3.2 Concurrent versus sequential therapy
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

## 2.22.1 What is the recommended treatment approach for the definitive management of patients with good performance status and inoperable stage III disease?

---

### 2.22.1.1 Introduction

Patients with stage III NSCLC may be deemed inoperable because of patient factors (the patient's respiratory function or co-morbidities may preclude operative intervention or the patient may choose not to proceed with surgery) or tumour factors (the extent or location of gross disease might make surgical resection technically impossible, for example some T4 tumours). Patients with N3 nodal involvement are not considered to be surgical candidates.<sup>[1]</sup>

The recommendations found in this section are applicable to good performance status patients with stage III disease who are inoperable because of patient or tumour factors.

[Back to top](#)

### 2.22.2.1 Surgery in inoperable N2 disease

The European Organization for the Research and Treatment of Cancer (EORTC) conducted a trial in which 579 patients with pathologically proven Stage IIIA-N2 disease deemed unresectable received three cycles of induction platinum-based chemotherapy. Patients demonstrating a radiological response (n=332) were then randomised to surgical resection or radiotherapy.<sup>[2]</sup> The guidelines for unresectability were: any N2 involvement by a non-squamous carcinoma and for a squamous cell carcinoma, any N2 nodal involvement exceeding level 4R for a right-sided tumour and level 5 and 6 for a left-sided tumour. Of the 154 patients (92% of those randomised) who underwent surgery post induction chemotherapy, 22 patients (14%) had an exploratory thoracotomy, 47% a pneumonectomy and 38% a lobectomy. Fifty percent of patients achieved a complete resection, of which 5% was a pathologically complete response. The operative mortality within 30 days was 4%. Postoperative radiotherapy was administered to 62 (40%) patients. The median and five-year OS survival for patients randomly assigned to resection versus radiotherapy were not significantly different at 16.4m versus 17.5m and 15.7% v 14% respectively (HR=1.06, 95% CI = 0.84-1.35). The authors concluded that surgery did not improve survival after a radiological response to induction chemotherapy in patients with unresectable stage IIIA-N2 NSCLC as compared with radiotherapy. RT was the preferred local treatment modality for these patients because of the lower morbidity and mortality.

[Back to top](#)

### 2.22.2 Defining operable and inoperable disease in stage III

---

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**Read full explanation**

### 2.22.2.2 Radiation therapy

Historically, radiation therapy alone was the standard therapy for inoperable stage III disease.

The Veterans Administration Lung Cancer Study Group which included 800 patients with advanced disease (including stage IV) found a small statistically significant survival advantage for radiotherapy compared to placebo.<sup>[3]</sup> For patient with inoperable stage IIIA/B disease treatment with conventional radiation therapy alone (60Gy in 30f) results in a median survival of 8-10 months and five year survival rates of between 5-8%.<sup>[4]</sup>

[Back to top](#)

### 2.22.2.3 Chemotherapy and radiation therapy

In an attempt to improve these outcomes and with patterns of relapse data demonstrating a high incidence of extrathoracic relapse, studies evaluating the role of systemic chemotherapy given in combination with RT, either sequentially or concurrently, were initiated.<sup>[5][6][7][8][9][10][11]</sup>

[Back to top](#)

#### 2.22.2.3.1 Radiation alone versus combination chemoradiotherapy

Several meta-analyses of these studies have been performed. The largest is the Non-small cell Lung Cancer Collaborative Group which analysed updated individual patient data from 22 trials in which 3033 patients were randomised to receive either RT alone or RT and chemotherapy given either sequentially or concurrently.<sup>[12]</sup> A variety of chemotherapy regimens were used. Eleven trials used cisplatin-containing regimens while the remaining trials used alkylating agents such as cyclophosphamide or nitrosourea in combination with methotrexate; vinca alkaloids or etoposide; or other regimens mainly based on doxorubicin. The results showed a significant overall benefit of chemotherapy with a hazard ratio of 0.90 (p=0.006), corresponding to an absolute survival benefit of 3% at two years and 2% at five years. Cisplatin-based regimens provided the strongest evidence for an effect in favour of chemotherapy with a hazard ratio of 0.87 (p=0.005) corresponding to an absolute benefit of 4% at two years and 2% at five years.

The Meta-Analysis of Cisplatin/Carboplatin Based Concomitant Chemotherapy in Non-Small Cell Lung Cancer (MAC3-LC) Group analysed individual patient data from nine trials including 1764 patients randomised to either RT alone or RT alone combined with concurrent cisplatin- or carboplatin-based chemotherapy.<sup>[13]</sup> The administration of platin-based chemotherapy and radiotherapy was associated with a hazard ratio of death of 0.89 (95% confidence interval, 0.81-0.98, p=0.02) compared to RT alone, corresponding to an absolute benefit of chemotherapy of 4% at two years. However, the authors stated that the results needed to be interpreted cautiously owing to heterogeneity across trials.

The Cochrane Collaboration has recently published an updated review of 19 randomised studies of concurrent chemoradiotherapy versus radiotherapy alone including 2728 patients.<sup>[14]</sup> Sixteen of the included studies used platinum-based chemotherapy regimens. The addition of chemotherapy to radiotherapy significantly reduced the overall risk of death, with a hazard ratio of 0.71 (95% confidence intervals 0.64-0.80), corresponding to an absolute survival benefit at two years of 8%. This was achieved at the expense of increased toxicity (acute oesophagitis, neutropenia and anaemia).

These meta-analyses demonstrated a survival benefit for the addition of chemotherapy to radiotherapy in the management of locally advanced non-small cell lung cancer.

The question of the optimal sequencing of the two treatment modalities ie sequential or concurrent administration was the subject of further studies.<sup>[9][10][11]</sup>

[Back to top](#)

### 2.22.2.3.2 Concurrent versus sequential therapy

The Non-small cell Lung Cancer Collaborative Group has performed a meta-analysis of six randomised trials (including individual patient data from 1205 patients) comparing concurrent versus sequential chemoradiotherapy administration.<sup>[15]</sup> The concurrent administration of chemoradiotherapy demonstrated a statistically significant survival benefit over sequential administration with a hazard ratio of 0.84 (95% confidence interval 0.74-0.95, p=0.004), corresponding to an absolute benefit of 5.7% at three years and 4.5% at five years. This survival benefit was thought to be due to a significant reduction in locoregional failures with concurrent chemoradiotherapy (hazard ratio 0.77, 95%CI 0.62-0.95; p=.01) corresponding to an absolute decrease of 6.0% at three years and 6.1% at five years. There was no difference between the two arms with respect to distant progression. The concurrent administration of chemoradiotherapy was associated with a significant increase in oesophageal toxicity, but not pulmonary toxicity.

The previously mentioned Cochrane review also performed a meta-analysis of six trials (1024 patients) of concurrent versus sequential chemoradiotherapy. Again, a significant overall survival benefit for concurrent treatment was observed (HR 0.74, 95%CI 0.62-0.89), representing a 10% survival benefit at two years.<sup>[14]</sup>

This data provides strong support for the concurrent administration of chemotherapy and radiation as the standard of care for inoperable stage III disease.

The survival advantage with concurrent administration is at the expense of an increased incidence of grade 3 to 4 oesophageal toxicity.

It is important to note that the majority of patients included in these studies were of good performance status. In many studies patients with weight loss  $\geq 5\%$  were excluded and elderly patients were poorly represented.

[Back to top](#)

## 2.22.3 Evidence summary and recommendations

Evidence summary	Level	References
In good performance status patients with inoperable stage III NSCLC, surgery does not improve survival in patients who have a radiologic response to induction chemotherapy compared with radiotherapy.	I	[15]
In good performance status patients with inoperable stage III NSCLC, the addition of chemotherapy to radiation therapy is associated with a statistically significant	I	[13], [12], [14]

Evidence summary	Level	References
survival benefit compared with radiation therapy alone		
In good performance status patients with inoperable stage III NSCLC, the concurrent administration of chemotherapy and radiation therapy provides a statistically significant survival benefit compared with the sequential administration of chemotherapy then radiation therapy.	I	[15], [14]

Evidence-based recommendation	Grade
For patients with good performance status and inoperable stage III NSCLC, the concurrent administration of chemotherapy and radiotherapy is recommended.	<b>A</b>

Practice point
In stage III NSCLC patients deemed inoperable at the time of diagnosis, the recommended treatment approach is concurrent chemoradiotherapy. Evidence suggests that the optimal chemotherapy regimen to give concurrently with radiation therapy is a platinum-based doublet.

Practice point
In patients with good performance status and inoperable stage III NSCLC in whom chemotherapy is contraindicated, treatment with a radical dose of radiation therapy alone is a reasonable option.

Back to top

## 2.22.4 References

1. ↑ Jett JR, Schild SE, Keith RL, Kesler KA, American College of Chest Physicians. *Treatment of non-small cell lung cancer, stage IIIB: ACCP evidence-based clinical practice guidelines (2nd edition)*. Chest 2007 Sep; 132(3 Suppl):266S-276S Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17873173>.
2. ↑ .
3. ↑ Wolf J, Patno ME, Roswit B, D'Esopo N. *Controlled study of survival of patients with clinically inoperable lung cancer treated with radiation therapy*. Am J Med 1966 Mar;40(3):360-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/4160252>.



4. ↑ Perez CA, Bauer M, Edelstein S, Gillespie BW, Birch R. *Impact of tumor control on survival in carcinoma of the lung treated with irradiation*. Int J Radiat Oncol Biol Phys 1986 Apr;12(4):539-47 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3009368>.
5. ↑ Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR. *Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial*. J Natl Cancer Inst 1996 Sep 4;88(17):1210-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8780630>.
6. ↑ Sause W, Kolesar P, Taylor S IV, Johnson D, Livingston R, Komaki R, et al. *Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group*. Chest 2000 Feb;117(2):358-64 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10669675>.
7. ↑ Schaake-Koning C, van den Bogaert W, Dalesio O, Festen J, Hoogenhout J, van Houtte P, et al. *Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer*. N Engl J Med 1992 Feb 20;326(8):524-30 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1310160>.
8. ↑ Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M, et al. *Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients*. J Natl Cancer Inst 1991 Mar 20;83(6):417-23 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1847977>.
9. ↑ <sup>9.0</sup> <sup>9.1</sup> Curran W, Scott C, Langer C et al.,. *Long-term benefits is observed in a phase III comparison of sequential v concurrent chemo-radiation for patients with unresectable stage III NSCLC*. Proc Am Soc clin Oncol 2003;22: 621.
10. ↑ <sup>10.0</sup> <sup>10.1</sup> Furuse K, Fukuoka M, Kawahara M, Nishikawa H, Takada Y, Kudoh S, et al. *Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer*. J Clin Oncol 1999 Sep;17(9):2692-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10561343>.
11. ↑ <sup>11.0</sup> <sup>11.1</sup> Pierre F, Maurice P, Gilles R et al.,. *A randomised phase iii trial of sequential chemoradiotherapy versus concurrent chemoradiotherpay in locally advanced non-small cell lung cancer (NSCLC) (GLOT-GFPCNPC95-01*. Proc Am Soc Clin Oncol 2001;20:312A.
12. ↑ <sup>12.0</sup> <sup>12.1</sup> Non-small Cell Lung Cancer Collaborative Group. *Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials*. BMJ 1995; 311(7010):899-909 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7580546>.
13. ↑ <sup>13.0</sup> <sup>13.1</sup> Aupérin A, Le Péchoux C, Pignon JP, Koning C, Jeremic B, Clamon G, et al. *Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients*. Ann Oncol 2006 Mar;17(3):473-83 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16500915>.
14. ↑ <sup>14.0</sup> <sup>14.1</sup> <sup>14.2</sup> <sup>14.3</sup> O'Rourke N, Roqué I Figuls M, Farré Bernadó N, Macbeth F. *Concurrent chemoradiotherapy in non-small cell lung cancer*. Cochrane Database Syst Rev 2010 Jun 16;(6):CD002140 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20556756>.
15. ↑ <sup>15.0</sup> <sup>15.1</sup> <sup>15.2</sup> .

Back to top



## 2.22.5 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.23 Optimal radiation dose and fractionation schedule

---

### Contents

- 1 What is the optimal radiation dose and fractionation schedule for good performance status patients with inoperable stage III NSCLC undergoing curative therapy?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Radiation dose
    - 2.1.1 Radiation dose fractionation schedules
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

### 2.23.1 What is the optimal radiation dose and fractionation schedule for good performance status patients with inoperable stage III NSCLC undergoing curative therapy?

---

#### 2.23.1.1 Introduction

Despite improved survival with the concurrent administration of chemotherapy and radiotherapy in stage III NSCLC, loco-regional recurrence rates remain high and survival figures remain low.<sup>[1]</sup> Attempts to improve loco-regional control and survival include radiation dose escalation using either conventional or altered fractionation schedules.

[Back to top](#)

## 2.23.2 Defining operable and inoperable disease in stage III

---

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**Read full explanation**

### 2.23.2.1 Radiation dose

#### 1) Loco-regional control

Evidence exists for a radiation dose-response relationship in NSCLC. The Radiation Therapy Oncology Group (RTOG) randomised patients with stage II and III disease (T1-3, N0-2) to either 40Gy total dose given in a split-course (4Gy/day for five days, followed by a two week break and a further 4Gy/day for five days), or a total dose of 40Gy, 50Gy or 60Gy given continuously (2Gy/day).<sup>[2]</sup> The highest doses resulted in significantly better local control rates, although there was no significant difference in survival. This study established 60Gy in 30f (2Gy/f/day) as the standard RT dose fractionation regimen in the definitive management of stage III disease.

However, the conventional dose of 60Gy is unlikely to control a significant proportion of tumours. At the University of Michigan doses were escalated from 63Gy to 84Gy using 1.8-2Gy fractions given five days a week. The best-fit logistic curve to the outcome data demonstrated that the radiation dose likely to produce 50% local progression-free survival at 30 months was 84.5Gy.<sup>[3]</sup> This data suggests that much higher biologically effective doses (BED) must be given in order to achieve a tumour control probability of greater than 50%.

#### 2) Survival

Radiation dose has been found to be a significant prognostic factor for overall survival (OS), in addition to locoregional control, in patients with locally advanced or medically inoperable early-stage NSCLC. A prospective dose-escalation trial in patients with stage I-III disease showed a positive relationship between dose and OS, as well as loco-regional tumour control, with RT doses in the range of 63-103Gy.<sup>[4]</sup> A retrospective review of 237 patients with stage III NSCLC treated with either RT alone or RT combined with chemotherapy demonstrated that the effect of higher radiation doses on survival was independent of whether chemotherapy was given.<sup>[5]</sup>

Early phase I/II data suggest that increasing the radiation dose to 74Gy can improve median survival times to 24 months.<sup>[6][7][8][9][10]</sup>

Currently, the commonly prescribed dose for definitive RT is 60-70Gy in 1.8-2.0Gy/f.<sup>[11]</sup>

The role of high dose RT with concurrent chemo was tested in a phase III RCT (RTOG 0617). This trial randomised patients with stage IIIA/B disease to either 60 or 74Gy in conjunction with either carboplatin and paclitaxel or carboplatin, paclitaxel and cetuximab.<sup>[12]</sup> The trial was designed to detect a median overall survival improvement of seven months in the high dose group. A planned interim analysis after 90 deaths found the high dose radiation therapy group had crossed the futility boundary and this arm has been closed to further accrual.<sup>[13]</sup>

[Back to top](#)

### **2.23.2.1.1 Radiation dose fractionation schedules**

Prolongation of overall treatment time is detrimental to tumour control and survival in NSCLC. Prolongation of time to complete treatment was associated with significantly shortened survival ( $p=0.016$ ) in four RTOG prospective randomised trials.<sup>[10]</sup> The loss of survival rate was 1.6% per day of prolongation beyond six weeks.<sup>[14]</sup> This rate of loss of survival probability in NSCLC is approximately as fast as the loss of local control with treatment prolongation in head and neck tumours. This implies that clonogenic cells continue to proliferate during treatment of NSCLC in a manner similar to those in head and neck cancer.

Thus, both total radiation dose and treatment duration (or overall time) are important in the outcome of radiotherapy in the management of NSCLC. Attempts to improve the outcomes have involved the manipulation of the distribution of radiation dose over time using altered fractionation schedules.

Accelerated radiotherapy delivers the same total dose over a shortened overall treatment time by using multiple daily fractions of standard fraction size. The aim is to reduce the repopulation of tumour cells during a conventional course of radiotherapy, thereby increasing the probability of tumour control for a given total dose. However, normal tissues also have less time to regenerate and thus the potential for acute normal tissue toxicity is increased. This can be overcome by giving multiple fractions per day with a reduced dose/fraction and a sufficient interfraction interval to allow for repair of normal tissues -so called hyperfractionated radiotherapy. A hybrid approach of accelerated fractionation and hyperfractionation is termed accelerated hyperfractionated RT.

Continuous hyperfractionated accelerated radiotherapy (CHART) has been compared with a conventional schedule of radiotherapy in a randomised trial in good performance status patients with inoperable NSCLC.<sup>[15]</sup> <sup>[16]</sup> The CHART regimen delivered 1.5Gy three times a day for 12 consecutive days to a total dose of 54Gy in 36f. The conventional radiotherapy regimen delivered 2Gy once a day, five days a week to a total dose of 60Gy in 30f. Between 1990 and 1995, 563 patients were recruited of whom 61% had stage IIIA or IIIB disease. Compared with conventional RT, CHART was associated with an absolute improvement in two year survival of 9% ( $p=0.008$ ). In the subgroup of patients with squamous cell histology, which accounted for 81% of all cases, there was an absolute improvement in two year survival of 13% from 20% to 33% ( $p=0.0007$ ). This group also demonstrated 25% reduction in the relative risk of local and/or distant disease ( $p=0.025$ ) and a 24% reduction in the relative risk of metastasis ( $p=0.043$ ). Severe dysphagia occurred more often in the CHART group than in the conventional group (19% versus 3%) but there were no important differences in short or long-term morbidity.

Subsequently, the CHARTWEL (CHART weekend-less) regimen (60Gy in 40 fractions over 2.5 weeks) was developed to provide dose escalation in an attempt to improve loco-regional control. The CHARTWEL-trial (ARO 97-1) randomised 406 patients (of whom 83% had Stage IIIA or IIIB disease) to either CHARTWEL or 66Gy in 33 fractions over 6.5 weeks (conventional fractionation). There was no significant difference between the two arms in terms of two year overall survival, disease-free survival or locoregional control. Overall survival in both arms of the CHARTWEL trial was as good as the survival seen in the hyperfractionated arm of CHART.<sup>[17]</sup>

Altered fractionation radiotherapy schedules have also been combined with chemotherapy. In a randomised Phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG 2597), patients with good performance status and unresectable stage IIIA/B NSCLC received induction chemotherapy followed by either hyperfractionated accelerated RT (HART consisting of 1.5Gy three times a day with two weekend breaks, to a total dose of 57.6Gy) or conventional radiotherapy (64Gy in daily 2 Gy fractions)<sup>[18]</sup> The study closed prematurely having achieved 40% of its target accrual. The median survival for HART was 20.3 months with two and three year survival figures of 44% and 34% respectively, compared with a median survival of 14.9 months and two and three year survival figures of 24% and 14% for conventional RT. These results did not achieve statistical significance.

Ball et al randomised 204 patients with inoperable stage I-III NSCLC to either one of four treatments using a 2x 2 factorial design: conventional RT (60Gy in 30f in six weeks), accelerated RT (60Gy in 30f in three weeks); or the same regimens with the addition of concurrent chemotherapy. There was no statistically significant difference in survival between treatment arms.<sup>[19]</sup>

The North Central Cancer Treatment Group (NCCTG) randomised 110 patients with PS  $\leq$  1 and stage IIIA/B NSCLC to either standard fractionated RT (60Gy in 30f) or hyperfractionated RT (1.5Gy twice daily to a total dose of 60Gy, with a two week break after the initial 30Gy). The hyperfractionated treatment was given with or without chemotherapy. There was no statistically significant difference in the rates of local recurrence or survival between the arms.<sup>[20]</sup>

A second NCCTG trial randomised 246 patients with stage III NSCLC and ECOG PS  $\leq$  1 to either conventional radiotherapy (60Gy in 30 daily fractions) or hyperfractionated RT ( 1.5Gy twice daily to a total dose of 60Gy, with a two week break after the initial 30Gy).<sup>[21]</sup> In this trial both treatment arms received concurrent chemotherapy. There were no significant differences in time to progression, overall survival or toxicity between the two arms. However, the use of split-course radiotherapy potentially allows for repopulation of tumour clonogens during the treatment break and is therefore deemed a suboptimal mode of RT delivery.

The RTOG 88-08 trial randomised 452 patients with stage III NSCLC, good performance status and <5% weight loss to receive either conventional radiotherapy alone, or sequentially administered chemotherapy and conventional radiotherapy or hyperfractionated RT (1.2Gy bd to a total dose of 69.6Gy).<sup>[22]</sup> This hyperfractionated RT regimen was derived from a preceding RTOG dose escalation study.<sup>[23]</sup> Sequential chemo-RT resulted in a statistically significant survival benefit compared with RT alone but there was no significant difference in survival between the sequential chemo-RT and hyperfractionated RT arms (median survival 13.2m versus 12m, two year survival 32% versus 24%,  $p=0.08$  for chemo-RT and chemo-hyperfractionated RT respectively).

The RTOG 94-10 trial randomised patients to sequential chemotherapy and conventional RT (once daily fractions to a total dose of 63Gy) or concurrent chemotherapy and conventional RT (once daily RT to 63Gy) or concurrent chemotherapy and hyperfractionated RT (twice-daily RT to 69.6Gy).<sup>[24]</sup> Survival was significantly better in the concurrent chemo-RT arm compared with the sequential chemo-RT arm (median survival 17m versus 14.6m,  $p=0.046$ ) but there was no significant survival difference between the chemo-conventional RT arm and chemo-hyperfractionated RT arm. However, acute toxicity was worst in the concurrent chemo-hyperfractionated RT arm.

In conclusion, there is evidence that CHART is superior to conventionally fractionated RT in patients with stage III NSCLC. However, the pure CHART schedule has not been directly compared with the concurrent administration of chemotherapy and conventionally fractionated RT. Hyperfractionated regimens administered alone or in combination with chemotherapy have not been shown to be superior to concurrently administered chemotherapy and conventionally fractionated RT regimens, although toxicity is increased. Furthermore, hyperfractionated regimens are labour-intensive and difficult to implement when resources are limited. Thus, the administration of once daily, conventionally fractionated RT in combination with chemotherapy is recommended as the standard of care.

[Back to top](#)

### 2.23.3 Evidence summary and recommendations

Evidence summary	Level	References
A radiation dose- response relationship exists for NSCLC	II	[2]
Radiation dose is a prognostic factor for OS in NSCLC	III-2	[4]
The radiation dose used in the definitive management of stage III disease should be at least 60Gy (assuming that dose-volume constraints on organs at risk are met).	II	[2]

Evidence-based recommendation	Grade
It is recommended that for patients with inoperable stage III NSCLC undergoing curative therapy once daily thoracic RT to at least 60Gy in 2Gy/f plus chemotherapy is administered.	<b>B</b>

Evidence summary	Level	References
Prolongation of overall treatment time is detrimental to tumour control and survival in NSCLC.	III-2	[10]
CHART is associated with a survival advantage compared with conventional RT	II	[15], [16]

Evidence summary	Level	References
alone. This survival advantage was most pronounced in patients with squamous cell histology.		
Accelerated RT given with chemotherapy, either sequentially or concurrently is not associated with a survival advantage over conventional RT given with chemotherapy, either sequentially or concurrently.	II	[19], [18]
Hyperfractionated RT given either alone or with chemotherapy is not associated with a survival advantage over conventional RT given either sequentially or concurrently with chemotherapy.	II	[20], [24], [22], [21]

Evidence-based recommendation	Grade
For patients with stage III NSCLC who are suitable for curative therapy, but where chemotherapy is contra-indicated or refused, CHART may be used as an alternative to radical conventionally fractionated radiotherapy.	<b>B</b>

Back to top

## 2.23.4 References

1. ↑ Mac Manus MP, Hicks RJ, Matthews JP, Wirth A, Rischin D, Ball DL. *Metabolic (FDG-PET) response after radical radiotherapy/chemoradiotherapy for non-small cell lung cancer correlates with patterns of failure.* Lung Cancer 2005 Jul;49(1):95-108 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15949595>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> <sup>2.2</sup> Perez CA, Bauer M, Edelstein S, Gillespie BW, Birch R. *Impact of tumor control on survival in carcinoma of the lung treated with irradiation.* Int J Radiat Oncol Biol Phys 1986 Apr;12(4):539-47 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3009368>.
3. ↑ Martel MK, Ten Haken RK, Hazuka MB, Kessler ML, Strawderman M, Turrisi AT, et al. *Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients.* Lung Cancer 1999 Apr;24(1):31-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10403692>.
4. ↑ <sup>4.0</sup> <sup>4.1</sup> .
5. ↑ Wang L, Correa CR, Zhao L, Hayman J, Kalemkerian GP, Lyons S, et al. *The effect of radiation dose and chemotherapy on overall survival in 237 patients with Stage III non-small-cell lung cancer.* Int J Radiat Oncol Biol Phys 2009 Apr 1;73(5):1383-90 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18929449>.
6. ↑ Bradley J, Graham M, Suzanne S, Byhardt R, Govindan R, Fowler J et al.,. *Phase I results of RTOG 0117: A phase I/II dose intensification study using 3DCRT and concurrent chemotherapy for patients with inoperable non-small cell lung cancer.* J Clin Oncol 2005;23: 16S, 7063 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20368547>.

7. ↑ Schild SE, McGinnis WL, Graham D, Hillman S, Fitch TR, Northfelt D, et al. *Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer.* Int J Radiat Oncol Biol Phys 2006 Jul 15;65(4):1106-11 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16730134>.
8. ↑ Rosenman JG, Halle JS, Socinski MA, Deschesne K, Moore DT, Johnson H, et al. *High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: technical issues and results of a phase III trial.* Int J Radiat Oncol Biol Phys 2002 Oct 1;54(2):348-56 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12243807>.
9. ↑ Blackstock A. *Cancer and Leukemia Group B: Induction plus concurrent chemotherapy with high-dose (74Gy) 3 dimensional (3-D) thoracic radiotherapy in stage III non-small cell lung cancer. Preliminary report of CALGB 30105.* Pro Amer Soc Clin Oncol 2006;24(1);7042.
10. ↑ <sup>10.0 10.1 10.2</sup> Cox JD, Pajak TF, Asbell S, Russell AH, Pederson J, Byhardt RW, et al. *Interruptions of high-dose radiation therapy decrease long-term survival of favorable patients with unresectable non-small cell carcinoma of the lung: analysis of 1244 cases from 3 Radiation Therapy Oncology Group (RTOG) trials.* Int J Radiat Oncol Biol Phys 1993 Oct 20;27(3):493-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8226140>.
11. ↑ Kong F, Gaspar, Komaki, Sun a , Bonner J, Choy H et al,. *Patterns of Practice in Radiation Dose Prescription and Treatment planning for patients with lung cancer among members of American Society of Therapeutic Radiology and Oncology.* Int J Radiat Oncol Biol Phys 2007;69(Suppl1):S483.
12. ↑ Bradley J, Schild S, Bogart J et al,. *RTOG 0617/NCCTG N0628/CALGB 30609/ECOG R0617: A randomised phase III comparison of standard-dose (60Gy) versus high-dose (74Gy) conformal radiotherapy with concurrent and consolidation carboplatin/paclitaxel +/- cetuximab in patients with Stage IIIA/B non-small cell lung cancer.*
13. ↑ Bradley J, Paulus R, Komaki R et al. *A randomised phase III comparison of standard dose (60Gy) v high dose (74Gy) conformal chemo-radiotherapy +/- cetuximab in Stage IIIA/B NSCLC: preliminary findings on radiation dose in RTOG 0617.* Proc ASTRO 2011.
14. ↑ Fowler JF, Chappell R. *Non-small cell lung tumors repopulate rapidly during radiation therapy.* Int J Radiat Oncol Biol Phys 2000 Jan 15;46(2):516-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10661362>.
15. ↑ <sup>15.0 15.1</sup> Saunders M, Dische S, Barrett A, Harvey A, Gibson D, Parmar M. *Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial. CHART Steering Committee.* Lancet 1997 Jul 19;350(9072):161-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9250182>.
16. ↑ <sup>16.0 16.1</sup> Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Parmar M. *Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee.* Radiother Oncol 1999 Aug;52(2):137-48 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10577699>.
17. ↑ Baumann M, Herrmann T, Koch R, Matthiessen W, Appold S, Wahlers B, et al. *Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC).* Radiother Oncol 2011 Jul; 100(1):76-85 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21757247>.
18. ↑ <sup>18.0 18.1</sup> .



19. ↑ <sup>19.0</sup> <sup>19.1</sup> Ball D, Bishop J, Smith J, O'Brien P, Davis S, Ryan G, et al. *A randomised phase III study of accelerated or standard fraction radiotherapy with or without concurrent carboplatin in inoperable non-small cell lung cancer: final report of an Australian multi-centre trial.* *Radiother Oncol* 1999 Aug;52(2):129-36 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10577698>.
20. ↑ <sup>20.0</sup> <sup>20.1</sup> Bonner JA, McGinnis WL, Stella PJ, Marschke RF Jr, Sloan JA, Shaw EG, et al. *The possible advantage of hyperfractionated thoracic radiotherapy in the treatment of locally advanced nonsmall cell lung carcinoma: results of a North Central Cancer Treatment Group Phase III Study.* *Cancer* 1998 Mar 15; 82(6):1037-48 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9506347>.
21. ↑ <sup>21.0</sup> <sup>21.1</sup> Schild SE, Stella PJ, Geyer SM, Bonner JA, Marks RS, McGinnis WL, et al. *Phase III trial comparing chemotherapy plus once-daily or twice-daily radiotherapy in Stage III non-small-cell lung cancer.* *Int J Radiat Oncol Biol Phys* 2002 Oct 1;54(2):370-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12243810>.
22. ↑ <sup>22.0</sup> <sup>22.1</sup> Sause W, Kolesar P, Taylor S IV, Johnson D, Livingston R, Komaki R, et al. *Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group.* *Chest* 2000 Feb;117(2):358-64 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10669675>.
23. ↑ Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF. *A randomized phase III trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11.* *J Clin Oncol* 1990 Sep;8(9):1543-55 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2167952>.
24. ↑ <sup>24.0</sup> <sup>24.1</sup> Curran W, Scott C, Langer C, Komaki R, Lee JS, Hauseret S et al.,. *Phase III comparison of sequential v concurrent chemoradiation for patients with unresected stage III non-small cell lung cancer (NSCLC): initial Report of Radiation Therapy Oncology Group (RTOG) 9410.* *Proc Am Soc Clin Oncol* 2000; 19:abstr 1891 Available from: [http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=2&abstractID=201631](http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=2&abstractID=201631).

[Back to top](#)

## 2.23.5 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				



[Back to top](#)

## 2.24 Principles of radiation therapy

---

### Contents

- 1 What are the principles of radiation therapy in the definitive management of stage III inoperable NSCLC?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Radiotherapy simulation
  - 2.2 Tumour mobility
  - 2.3 Target volume definition
  - 2.4 Critical structure dose constraints
    - 2.4.1 Lung
    - 2.4.2 Spinal cord
    - 2.4.3 Oesophagus
    - 2.4.4 Heart
    - 2.4.5 Brachial plexus
  - 2.5 Treatment planning and delivery
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

### 2.24.1 What are the principles of radiation therapy in the definitive management of stage III inoperable NSCLC?

---

#### 2.24.1.1 Introduction

Improved accuracy in target volume delineation and radiation therapy delivery has the potential to improve treatment outcomes in NSCLC by facilitating radiation dose escalation and ensuring geographic misses are avoided.

[Back to top](#)

## 2.24.2 Defining operable and inoperable disease in stage III

---

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**Read full explanation**

### 2.24.2.1 Radiotherapy simulation

Patients should be simulated in the treatment position using an immobilisation device to ensure random and systematic set-up errors are minimised.<sup>[1]</sup> Treatment planning should be performed using CT scans. The scan should encompass the entire lung volume to ensure accurate calculation of dose volume histograms (DVHs). The CT scan slice thickness should be 2-3mm to allow the generation of high resolution digitally reconstructed radiographs (DRR).<sup>[2]</sup> The use of CT-based treatment planning is associated with a survival advantage in a non-randomised population based study.<sup>[3]</sup>

Intravenous contrast may assist in target delineation especially in tumours which are centrally located or associated with nodal disease.<sup>[4]</sup>

[Back to top](#)

### 2.24.2.2 Tumour mobility

In contrast to tumours at other anatomic sites, lung tumours generally move with breathing. In addition, tumour motion is not uniform in three dimensions and the degree of movement may be dependent upon the location of the tumour in the lungs and on the compliance of the thorax and lung parenchyma.<sup>[5][6][7]</sup> Thus, the application of “standard margins” around tumours to account for mobility can lead to geographic miss and unnecessary normal tissue irradiation.<sup>[8][9]</sup> The use of planning methods to evaluate and account for tumour motion is recommended.<sup>[10]</sup>

Acceptable methods, according to the AAPM Task Group 76 guideline,<sup>[10]</sup> include:

1. Motion-encompassing methods such as slow CT scanning, inhale and exhale breath-hold CT, four-dimension (4-D) respiration-correlated CT.
2. Respiratory gating methods using an external respiration signal or using internal fiducial markers.
3. Motion-limiting methods including breath-hold by deep-inspiration breath-hold, active-breathing control (ABC) device, self breath-hold without respiratory monitoring or
4. Forced shallow breathing with abdominal compression.
5. Real-time tumour- tracking

---

[Back to top](#)

### 2.24.2.3 Target volume definition

The Gross Tumour Volume (GTV) is defined as the visible disease (both primary and nodal) on CT and/or CT-PET.<sup>[11]</sup> The measured diameter of tumours in lung parenchyma and mediastinum is dependent on the window width and level chosen to analyse CT slices.<sup>[12]</sup> The appropriate window settings should be used when contouring the parenchymal and nodal disease. Lymph nodes with a short axis diameter  $\geq 1$ cm are generally considered pathological and should be included in the GTV unless metastases have been excluded by histological examination following mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration or PET scanning.<sup>[13][14]</sup>

The use of PET scans in helping to delineate tumour volumes is encouraged. The incorporation of FDG-PET information into CT-based planning systems changes target volumes and radiotherapy fields in a significant proportion of patients.<sup>[15]</sup> FDG-PET scans enable more accurate differentiation of viable tumour tissue from surrounding consolidated lung,<sup>[15]</sup> are superior to CT scans in demonstrating mediastinal node involvement<sup>[16]</sup> and reduce inter-observer variability in delineating target volumes.<sup>[17]</sup> However, there is no data demonstrating an improvement in survival or local recurrence with the incorporation of PET data into CT-based planning.<sup>[18]</sup> A single institution study of serial PET scans in patients with untreated, predominantly Stage III NSCLC demonstrated a 32% probability of tumour upstaging with a 24 day interscan interval. Thus consideration should be given to repeating the PET scan if the interval between the staging PET scan and the time of target volume delineation is long.<sup>[19]</sup>

The Clinical Target Volume (CTV) encompasses the GTV plus an anatomically defined area thought to harbour micrometastases.<sup>[11]</sup> Giroud et al performed a quantitative assessment of microscopic extension on histological slides from “well insufflated” resected NSCLC cases.<sup>[20]</sup> The authors found that a GTV to CTV margin of 8mm for adenocarcinoma and 6mm for squamous cell carcinoma had a 95% probability of covering microscopic extension.

The role of elective nodal irradiation (ENI), that is encompassing nodal regions that may be at risk of harbouring micro metastatic disease, is controversial.<sup>[21]</sup> It is argued that enlarging the irradiated volume to include nodal areas that might harbour microscopic disease is counterintuitive as it prevents safe dose escalation when currently employed radiation doses fail to sterilize the primary in a significant proportion of patients.

Only one randomised study has addressed the issue of omitting ENI. In a study from China, 200 patients with inoperable stage III NSCLC treated with concurrent chemo radiotherapy were randomised to either involved field radiotherapy (IFI) or ENI.<sup>[22]</sup> PET staging was not performed and patients in the IFI arm received a higher radiation dose (68-74Gy) than those in the ENI arm (60-64Gy). Patients in the IFI arm experienced a better overall response rate (90% versus 79%,  $p=0.032$ ), a better five-year local control rate (51% versus 36%,  $p=0.032$ ) and a lower incidence of radiation pneumonitis (17% versus 29%,  $p=0.044$ ) than those in the ENI arm. Only the two year survival rates were statistically significant but the study was not powered for a survival endpoint. It remains unclear whether the poorer outcome from ENI was due to the lower RT dose or the use of ENI.

Studies evaluating patterns of failure demonstrate that the use of involved field RT without ENI allows the radiation dose to be escalated with acceptable toxicity and a low risk of isolated nodal relapse (0%-8%).<sup>[23]</sup>

Furthermore, the incorporation of FDG-PET information may reduce the incidence of nodal failure further. Two studies have prospectively evaluated the incidence of isolated nodal failure when only lymph nodes metabolically active on PET scan were included in the GTV (ENI omitted).<sup>[24][23]</sup> The incidence of isolated nodal failure was 2% and 3% respectively. Both studies concluded that the target volumes should include the tumour and FDG-PET scan positive lymph nodes only.

The Planning Target Volume (PTV) encompasses the CTV plus a margin to account for tumour motion (the internal margin) and a margin to account for the inaccuracies of daily setup in fractionated radiotherapy (set-up margin)<sup>[11]</sup>

The internal margin should be determined by the modality used to measure or control tumour mobility.

The set-up margin should be determined by the individual institutions' estimation of the specific errors inherent in their process of radiotherapy planning and delivery.

[Back to top](#)

## **2.24.2.4 Critical structure dose constraints**

### **2.24.2.4.1 Lung**

There is a considerable volume of literature relating dose-volume parameters with the incidence of radiation pneumonitis. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report recommends the V20 (the volume of both lungs minus the PTV receiving 20Gy) be limited to  $\leq 30$  -35% and the Mean total lung dose (MLD) be limited to  $\leq 20$ -23Gy (with conventional fractionation) to limit the risk of radiation pneumonitis to  $\leq 20\%$  in definitely treated patients with NSCLC.<sup>[25]</sup>

[Back to top](#)

### **2.24.2.4.2 Spinal cord**

The QUANTEC report states that a total dose of 50Gy in conventional fractionation of 2Gy per day to the full cord cross-section, is associated with a 0.2% risk of myelopathy and a total dose of 60Gy is associated with a 6% risk of myelopathy.<sup>[26]</sup> The updated National Comprehensive Cancer Network Guidelines (NCCN) recommends a dose constraint of 50Gy in 1.8-2.0Gy/f for the spinal cord in conventionally fractionated 3D conformal RT in NSCLC.<sup>[27]</sup>

[Back to top](#)

### **2.24.2.4.3 Oesophagus**

The QUANTEC report was not able to identify a single best threshold volumetric parameter for oesophageal irradiation, because a wide range of V<sub>dose</sub> parameters correlated significantly with severe acute oesophagitis.<sup>[28]</sup> There was a clear trend demonstrating volumes receiving > 40-50Gy correlated significantly with acute oesophagitis.

Similarly, a systematic review of dose-volume parameters predicting the incidence of radiation-induced oesophagitis identified six dosimetric parameters that may be of value.<sup>[29]</sup> The ongoing Phase III Intergroup trial (RTOG 0617) has recommended (but not mandated) that the mean dose to the oesophagus be kept to <34Gy.<sup>[30]</sup> This recommendation is based on the Washington University retrospective review demonstrating a 100% risk of grade 3-5 acute oesophagitis if the mean oesophageal dose exceeded 34Gy.<sup>[31]</sup>

[Back to top](#)

### **2.24.2.4.4 Heart**

Acceptable volumetric parameters for cardiac irradiation have not been well studied in the setting of NSCLC treatment

The following limits are recommended in the RTOG 0617 trial, based on the recommendations of Emami:<sup>[32]</sup> the volume receiving 60Gy ( $V_{60}$ ) <33%,  $V_{45}$  <67%

### **2.24.2.4.5 Brachial plexus**

Brachial plexus doses should be kept <66Gy in 1.8-2.0Gy/f.<sup>[30]</sup>

[Back to top](#)

### **2.24.2.5 Treatment planning and delivery**

Three-dimensional (3D) treatment planning is essential in order to ensure adequate tumour coverage and to optimise the sparing of normal tissues.<sup>[33]</sup>

The photon beam energy should be individualised. In general, a photon beam energy between 4-10MV is recommended.<sup>[27]</sup>

The use of methods to account for tumour motion is highly recommended (as above).

New radiotherapeutic techniques such as intensity-modulated radiation therapy (IMRT), tomotherapy and proton beam therapy are currently being evaluated.

A retrospective review from the MD Anderson Cancer Centre comparing disease outcomes and toxicity in patients treated with concomitant chemotherapy and either 4DCT/IMRT or CT/3DCRT demonstrated that 4DCRT /IMRT resulted in a significant reduction in toxicity and a significant improvement in OS compared with CT /3DCRT.<sup>[34]</sup>

[Back to top](#)

### 2.24.3 Evidence summary and recommendations

Evidence summary	Level	References
The use of an immobilisation device for patient simulation minimises set-up errors.	III-2	[1]

Evidence-based recommendation	Grade
Patients can be simulated in the treatment position using an immobilisation device.	<b>C</b>

Evidence summary	Level	References
The use of multi-slice CT scans and 3D treatment planning systems ensure optimal tumour coverage and normal tissue sparing compared with 2D planning.	III-2	[33], [3]
The use of CT-based treatment planning is associated with a survival advantage in a non-randomised population based study.		

Evidence-based recommendation	Grade
Treatment planning may utilise multi-slice CT image acquisition and a 3D planning system.	<b>C</b>

Practice point
Treatment planning may utilise an accepted method of evaluating and accounting for tumour motion.

Evidence summary	Level	References
The measured diameter of tumours in lung parenchyma and mediastinum is dependent on the window width and level chosen to analyse CT slices.	III-2	[12]

Evidence-based recommendation	Grade
The appropriate window settings may be used when contouring the parenchymal and nodal disease.	<b>C</b>

Practice point
Individual characteristics of breathing and variations associated with tumour location and pulmonary and tumour pathology lead to individual patterns of tumour motion.

Evidence summary	Level	References
FDG-PET scans enable more accurate differentiation of viable tumour tissue from surrounding consolidated lung, are superior to CT scans in demonstrating mediastinal node involvement and reduce inter-observer variability in delineating target volumes	I, II, III-2	[16], [15], [17]

Evidence-based recommendation	Grade
Tumour volume delineation may be assisted by the incorporation of FDG-PET information into the CT -based planning system.	<b>B</b>

Evidence summary	Level	References
Intravenous contrast may assist in target delineation especially in centrally located tumours or tumours associated with nodal disease.	III-2	[4]

Evidence-based recommendation	Grade
Tumour volume delineation may be assisted by the use of intravenous contrast during simulation.	<b>C</b>

Evidence summary	Level	References
A GTV to CTV margin of 8mm for adenocarcinoma and 6mm for squamous cell carcinoma has a 95% probability of covering microscopic tumour extension.	III-2	[20]

Evidence-based recommendation	Grade
The Clinical Target Volume may encompass the Gross Tumour Volume plus a margin of 6-8mm.	<b>C</b>

Practice point
<p>-The Gross Tumour Volume may encompass the visible disease (both primary and nodal) on CT and/or CT-PET.</p> <p>-The Clinical Target Volume may encompass the Gross Tumour Volume plus a margin to account for microscopic extension of disease .</p> <p>-The Planning Target Volume may encompass the Clinical Target Volume plus a margin to account for tumour motion (as determined by the individual institution's method of evaluating and accounting for tumour motion) and a margin to account for set-up error (as determined by the individual institutions' estimation of the specific errors inherent in their process of radiotherapy planning and delivery).</p>

Evidence summary	Level	References
The use of involved field RT without ENI allows the radiation dose to be escalated with acceptable toxicity and a low risk of isolated nodal relapse (0%-8%)	II, IV	[23] , [21] , [24] , [22]



Evidence-based recommendation	Grade
Elective nodal irradiation is not recommended.	<b>C</b>

Practice point
<p>Normal Tissue Dose Volume Constraints</p> <p>Limiting the lung V20 <math>\leq</math> 30-35% and the MLD <math>\leq</math>20-23Gy limits the risk of radiation pneumonitis to <math>\leq</math>20% in definitely treated patients with NSCLC.</p> <p>Lung: V20 <math>\leq</math> 30 -35% , Mean total lung dose (MLD) <math>\leq</math> 20-23Gy</p> <p>A total dose of 50Gy in 2Gy/f to the full spinal cord cross-section is associated with a 0.2% risk of myelopathy.</p> <p>Spinal Cord: 50Gy in 1.8-2.0Gy/f</p>

Practice point
<p>A single best threshold volumetric parameter for oesophageal irradiation has not been identified.</p>

Back to top

## 2.24.4 References

1. ↑ <sup>1.0</sup> <sup>1.1</sup> Halperin R, Roa W, Field M, Hanson J, Murray B. *Setup reproducibility in radiation therapy for lung cancer: a comparison between T-bar and expanded foam immobilization devices*. Int J Radiat Oncol Biol Phys 1999 Jan 1;43(1):211-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9989528>.
2. ↑ Van Sörnsen de Koste JR, de Boer HC, Schuchhard-Schipper RH, Senan S, Heijmen BJ. *Procedures for high precision setup verification and correction of lung cancer patients using CT-simulation and digitally reconstructed radiographs (DRR)*. Int J Radiat Oncol Biol Phys 2003 Mar 1;55(3):804-10 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12573768>.

3. ↑ <sup>3.0</sup> <sup>3.1</sup> Chen AB, Neville BA, Sher DJ, Chen K, Schrag D. *Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation.* J Clin Oncol 2011 Jun 10;29(17):2305-11 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21537034>.
4. ↑ <sup>4.0</sup> <sup>4.1</sup> McGibney C. *Impact of intravenous contrast on target definition in radiotherapy of non small cell lung cancer.* Eur J Cancer 2001;37(Suppl 6):211.
5. ↑ van Sörnsen de Koste JR, Lagerwaard FJ, Nijssen-Visser MR, Graveland WJ, Senan S. *Tumor location cannot predict the mobility of lung tumors: a 3D analysis of data generated from multiple CT scans.* Int J Radiat Oncol Biol Phys 2003 Jun 1;56(2):348-54 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12738308>.
6. ↑ Seppenwoolde Y, Shirato H, Kitamura K, Shimizu S, van Herk M, Lebesque JV, et al. *Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy.* Int J Radiat Oncol Biol Phys 2002 Jul 15;53(4):822-34 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12095547>.
7. ↑ Liu HH, Balter P, Tutt T, Choi B, Zhang J, Wang C, et al. *Assessing respiration-induced tumor motion and internal target volume using four-dimensional computed tomography for radiotherapy of lung cancer.* Int J Radiat Oncol Biol Phys 2007 Jun 1;68(2):531-40 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17398035>.
8. ↑ van Sörnsen de Koste JR, Lagerwaard FJ, Schuchhard-Schipper RH, Nijssen-Visser MR, Voet PW, Oei SS, et al. *Dosimetric consequences of tumor mobility in radiotherapy of stage I non-small cell lung cancer--an analysis of data generated using 'slow' CT scans.* Radiother Oncol 2001 Oct;61(1):93-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11578735>.
9. ↑ de Koste JR, Lagerwaard FJ, de Boer HC, Nijssen-Visser MR, Senan S. *Are multiple CT scans required for planning curative radiotherapy in lung tumors of the lower lobe?* Int J Radiat Oncol Biol Phys 2003 Apr 1;55(5):1394-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12654452>.
10. ↑ <sup>10.0</sup> <sup>10.1</sup> Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, et al. *The management of respiratory motion in radiation oncology report of AAPM Task Group 76.* Med Phys 2006 Oct;33(10):3874-900 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17089851>.
11. ↑ <sup>11.0</sup> <sup>11.1</sup> <sup>11.2</sup> International Commission of Radiation Units and Measurements. *Prescribing, Recording and Reporting Photon Beam Therapy. Report number 50.* Bethesda: ICRU; 1993.
12. ↑ <sup>12.0</sup> <sup>12.1</sup> Harris KM, Adams H, Lloyd DC, Harvey DJ. *The effect on apparent size of simulated pulmonary nodules of using three standard CT window settings.* Clin Radiol 1993 Apr;47(4):241-4 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8495570>.
13. ↑ Glazer GM, Gross BH, Quint LE, Francis IR, Bookstein FL, Orringer MB. *Normal mediastinal lymph nodes: number and size according to American Thoracic Society mapping.* AJR Am J Roentgenol 1985 Feb;144(2):261-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3871268>.
14. ↑ Kiyono K, Sone S, Sakai F, Imai Y, Watanabe T, Izuno I, et al. *The number and size of normal mediastinal lymph nodes: a postmortem study.* AJR Am J Roentgenol 1988 Apr;150(4):771-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3258087>.
15. ↑ <sup>15.0</sup> <sup>15.1</sup> <sup>15.2</sup> Mac Manus M, Hicks RJ. *The use of positron emission tomography (PET) in the staging /evaluation, treatment, and follow-up of patients with lung cancer: a critical review.* Int J Radiat Oncol Biol Phys 2008 Dec 1;72(5):1298-306 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19028270>.

16. ↑ <sup>16.0</sup> <sup>16.1</sup> Gould MK, Kuschner WG, Rydzak CE, Maclean CC, Demas AN, Shigemitsu H, et al. *Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis.* Ann Intern Med 2003 Dec 2;139(11):879-92 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14644890>.
17. ↑ <sup>17.0</sup> <sup>17.1</sup> Steenbakkers RJ, Duppen JC, Fitton I, Deurloo KE, Zijp LJ, Comans EF, et al. *Reduction of observer variation using matched CT-PET for lung cancer delineation: a three-dimensional analysis.* Int J Radiat Oncol Biol Phys 2006 Feb 1;64(2):435-48 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16198064>.
18. ↑ Ung Y, Bezjak A, Coakley N, Evans W, Lung Cancer Disease Site Group. *Positron Emission Tomography in Radiation Treatment Planning for Lung Cancer.* 2010 Available from: <http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/lung-ebst/>.
19. ↑ Everitt S, Herschtal A, Callahan J, Plumridge N, Ball D, Kron T, et al. *High rates of tumor growth and disease progression detected on serial pretreatment fluorodeoxyglucose-positron emission tomography/computed tomography scans in radical radiotherapy candidates with nonsmall cell lung cancer.* Cancer 2010 Nov 1;116(21):5030-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20623786>.
20. ↑ <sup>20.0</sup> <sup>20.1</sup> Giraud P, Antoine M, Larrouy A, Milleron B, Callard P, De Rycke Y, et al. *Evaluation of microscopic tumor extension in non-small-cell lung cancer for three-dimensional conformal radiotherapy planning.* Int J Radiat Oncol Biol Phys 2000 Nov 1;48(4):1015-24 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11072158>.
21. ↑ <sup>21.0</sup> <sup>21.1</sup> Belderbos JS, Kepka L, Spring Kong FM, Martel MK, Videtic GM, Jeremic B. *Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small-Cell lung cancer (NSCLC).* Int J Radiat Oncol Biol Phys 2008 Oct 1;72(2):335-42 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18793953>.
22. ↑ <sup>22.0</sup> <sup>22.1</sup> .
23. ↑ <sup>23.0</sup> <sup>23.1</sup> <sup>23.2</sup> Belderbos JS, Heemsbergen WD, De Jaeger K, Baas P, Lebesque JV. *Final results of a Phase I/II dose escalation trial in non-small-cell lung cancer using three-dimensional conformal radiotherapy.* Int J Radiat Oncol Biol Phys 2006 Sep 1;66(1):126-34 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16904518>.
24. ↑ <sup>24.0</sup> <sup>24.1</sup> De Ruyscher D, Wanders S, van Haren E, Hochstenbag M, Geeraedts W, Utama I, et al. *Selective mediastinal node irradiation based on FDG-PET scan data in patients with non-small-cell lung cancer: a prospective clinical study.* Int J Radiat Oncol Biol Phys 2005 Jul 15;62(4):988-94 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15989999>.
25. ↑ Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, et al. *Radiation dose-volume effects in the lung.* Int J Radiat Oncol Biol Phys 2010 Mar 1;76(3 Suppl):S70-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20171521>.
26. ↑ Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. *Radiation dose-volume effects in the spinal cord.* Int J Radiat Oncol Biol Phys 2010 Mar 1;76(3 Suppl):S42-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20171517>.
27. ↑ <sup>27.0</sup> <sup>27.1</sup> National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) Dermatofibrosarcoma Protuberans Version 1.2012.* 2011 Sep 27 Available from: [http://www.nccn.org/professionals/physician\\_gls/pdf/dfsp.pdf](http://www.nccn.org/professionals/physician_gls/pdf/dfsp.pdf).

28. ↑ Werner-Wasik M, Yorke E, Deasy J, Nam J, Marks LB. *Radiation dose-volume effects in the esophagus.* Int J Radiat Oncol Biol Phys 2010 Mar 1;76(3 Suppl):S86-93 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20171523>.
29. ↑ Rose J, Rodrigues G, Yaremko B, Lock M, D'Souza D. *Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy.* Radiother Oncol 2009 Jun;91(3):282-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18950881>.
30. ↑ <sup>30.0</sup> <sup>30.1</sup> Bradley J, Schild S, Bogart J et al.,. *RTOG 0617/NCCTG N0628/CALGB 30609/ECOG R0617: A randomised phase III comparison of standard-dose (60Gy0 versus high-dose (74Gy) conformal radiotherapy with concurrent and consolidation carboplatin/paclitaxel +/- cetuximab in patients with Stage IIIA/B non-small cell lung cancer.*
31. ↑ Singh AK, Lockett MA, Bradley JD. *Predictors of radiation-induced esophageal toxicity in patients with non-small-cell lung cancer treated with three-dimensional conformal radiotherapy.* Int J Radiat Oncol Biol Phys 2003 Feb 1;55(2):337-41 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12527046>.
32. ↑ Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. *Tolerance of normal tissue to therapeutic irradiation.* Int J Radiat Oncol Biol Phys 1991 May 15;21(1):109-22 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2032882>.
33. ↑ <sup>33.0</sup> <sup>33.1</sup> McGibney C, Holmberg O, McClean B, Williams C, McCrea P, Sutton P, et al. *Dose escalation of chart in non-small cell lung cancer: is three-dimensional conformal radiation therapy really necessary?* Int J Radiat Oncol Biol Phys 1999 Sep 1;45(2):339-50 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10487554>.
34. ↑ .

[Back to top](#)

## 2.24.5 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.25 Concurrent chemoradiotherapy best practice

### Contents

- 1 What is the optimal treatment approach for patients with stage III inoperable NSCLC who, because of patient or tumour factors, are not suitable for curative treatment with concurrent chemo-radiotherapy?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Radiotherapy
  - 2.2 Chemotherapy
  - 2.3 Combined modality therapy
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

### 2.25.1 What is the optimal treatment approach for patients with stage III inoperable NSCLC who, because of patient or tumour factors, are not suitable for curative treatment with concurrent chemo-radiotherapy?

#### 2.25.1.1 Introduction

Patients with inoperable NSCLC can be divided into three groups:<sup>[1]</sup>

1. Patients with good performance status (PS), adequate pulmonary function and localised tumour who should be considered for radical treatment with the accepted “standard of care” being the concurrent administration of chemotherapy and radiotherapy (RT) to doses  $\geq 60\text{Gy}$
2. Patients with poor PS, substantial weight loss ( $>10\%$ ) and advanced disease for whom simple palliative measures are appropriate; and

#### 2.25.2 Defining operable and inoperable disease in stage III

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**Read full explanation**

3. An intermediate group of patients who have a good PS but locally advanced disease for whom radical chemo-radiation ( $\geq 60\text{Gy}$ ) is not feasible either due to tumour extent or patient factors (such as poor respiratory function).

Recommendations in this section apply to patients in groups 2 and 3. In either group the aim of treatment is to palliate symptoms and maintain quality of life.

[Back to top](#)

### 2.25.2.1 Radiotherapy

The most common symptoms that are considered for palliation include dyspnoea, cough, haemoptysis and pain. A number of randomised controlled trials (RCTs) comparing different palliative RT regimens in locally advanced NSCLC have been performed. The characteristics of these trials and their results are summarised in the Table link below.

Table: Randomised controlled trials comparing different palliative RT regimens in locally advanced NSCLC

Two systematic reviews of these data have been undertaken. A Cochrane review of 14 RCTS involving 3576 evaluable patients found that palliative RT achieves reasonable rates of symptom control (haemoptysis, cough, pain, dyspnoea) but there was no difference in specific symptom control rates between lower dose and higher RT dose schedules.<sup>[2]</sup> The authors also concluded that there was strong evidence, from four studies<sup>[3][4][5][6]</sup> for an increase in survival (5% at one year and 3% at two years) in patients with good PS who were given higher dose RT.

A second systematic review performed a quantitative pooling of the results of 13 RCTS comparing different dose fractionation schedules of palliative thoracic RT in 3473 patients.<sup>[7]</sup> The authors confirmed the findings of the previous systematic review in terms of the equivalence of specific symptom palliation but reported that, in comparison with lower dose schedules, higher dose schedules ( $\geq 35\text{Gy}_{10}$  Biologically equivalent dose, BED) resulted in: a greater likelihood of symptom improvement on the total symptom score, a longer duration of symptom relief, an improvement in one year survival (26.5% versus 21.7%,  $p = 0.002$ ) and a higher incidence of toxicity, predominantly oesophagitis.

Both systematic reviews concluded that, given the possibility of an improvement in total symptom score and overall survival, higher dose palliative radiotherapy regimens should be considered for selected patients with good PS and locally advanced NSCLC. Short courses of palliative RT should be considered for poor PS patients. The following rates of palliation have been reported with higher dose palliative radiotherapy schedules: 79% for haemoptysis, 60% for chest pain, 48% for cough and 36% for dyspnoea.<sup>[8]</sup>

[Back to top](#)

### 2.25.2.2 Chemotherapy

In advanced NSCLC, systemic chemotherapy improves survival and maintains QOL compared with best supportive care. In a meta-analysis of 16 trials involving 2714 patients, chemotherapy reduced the risk of death (hazard ratio = 0.77; 95% CI 0.71-0.83;  $p \leq 0.0001$ ), resulting in an absolute improvement in one year survival of 9% (from 20% to 29%).<sup>[9]</sup> Studies which prospectively evaluate intrathoracic tumour-related symptoms demonstrate an improvement from baseline scores with palliative chemotherapy.<sup>[10]</sup>

[Back to top](#)

### 2.25.2.3 Combined modality therapy

Typically, palliative chemotherapy is delivered before or after palliative RT to avoid the toxicity of concurrent administration in the non-curative setting. Combining the two modalities in an attempt to improve local and distant disease control in this patient population is an area of ongoing research.

## 2.25.3 Evidence summary and recommendations

Evidence summary	Level	References
Palliative radiotherapy achieves reasonable rates of symptom control.	I	[2]

Evidence-based recommendation	Grade
For patients with stage III disease who because of performance status or disease extent are not suitable for treatment with curative intent and who are experiencing symptoms as a result of chest disease, palliative radiotherapy is recommended.	<b>A</b>

Evidence summary	Level	References
Higher radiation dose schedules result in a greater likelihood of symptom improvement, a longer duration of symptom relief and an improvement in one year survival compared with lower dose radiation schedules.	I	[2], [7]

Evidence-based recommendation	Grade
The radiation dose and fractionation pattern should be chosen on the basis of the patient's performance status:	<b>A</b>



Evidence-based recommendation	Grade
<p>- patients with good performance status should be treated with longer radiotherapy regimens because this will lead to a longer duration of symptom relief and may increase survival. Commonly employed radiotherapy regimens include 20Gy/5f, 30Gy/10f, 36Gy/12f, 40Gy/15f, 50Gy/20f.</p> <p>- patients with poor performance status should be treated with short courses of treatment. Commonly employed radiotherapy regimens include 10Gy/1f, 16Gy/2f (1f/week).</p>	

Evidence summary	Level	References
In advanced NSCLC, systemic chemotherapy improves survival and maintains QOL compared with best supportive care.	I	[9]

Evidence-based recommendation	Grade
For patients with stage III disease who because of performance status or disease extent are not suitable for treatment with curative intent and who are not experiencing symptoms specifically related to chest disease, referral for chemotherapy opinion should be considered.	<b>A</b>

Practice point
Given the symptomatology experienced by these patients with stage III disease and their poor survival outcomes, referral to palliative care services may be considered.

Back to top

## 2.25.4 References

1. ↑ Hoskin PJ. *Palliative radiotherapy for non-small-cell lung cancer: which dose?* Clin Oncol (R Coll Radiol) 2005 Feb;17(1):59-60 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15714932>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> <sup>2.2</sup> Lester JF, Macbeth FR, Toy E, Coles B. *Palliative radiotherapy regimens for non-small cell lung cancer*. Cochrane Database Syst Rev 2006 Oct 18;(4):CD002143 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17054152>.



3. ↑ Macbeth FR, Bolger JJ, Hopwood P, Bleehen NM, Cartmell J, Girling DJ, et al. *Randomized trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Medical Research Council Lung Cancer Working Party.* Clin Oncol (R Coll Radiol) 1996;8(3):167-75 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8814371>.
4. ↑ Reinfuss M, Glinski B, Kowalska T, Kulpa J, Zawila K, Reinfuss K, et al. *Radiotherapy for stage III, inoperable, asymptomatic small cell lung cancer. Final results of a prospective randomized study (240 patients).* Cancer Radiother 1999;3(6):475-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10630160>.
5. ↑ .
6. ↑ .
7. ↑ <sup>7.0</sup> <sup>7.1</sup> Fairchild A, Harris K, Barnes E, Wong R, Lutz S, Bezjak A, et al. *Palliative thoracic radiotherapy for lung cancer: a systematic review.* J Clin Oncol 2008 Aug 20;26(24):4001-11 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18711191>.
8. ↑ Langendijk JA, ten Velde GP, Aaronson NK, de Jong JM, Muller MJ, Wouters EF. *Quality of life after palliative radiotherapy in non-small cell lung cancer: a prospective study.* Int J Radiat Oncol Biol Phys 2000 Apr 1;47(1):149-55 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10758317>.
9. ↑ <sup>9.0</sup> <sup>9.1</sup> NSCLC Meta-Analyses Collaborative Group. *Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials.* J Clin Oncol 2008 Oct 1;26(28):4617-25 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18678835>.
10. ↑ Georgoulas V, Ardavanis A, Agelidou A, Agelidou M, Chandrinou V, Tsaroucha E, et al. *Docetaxel versus docetaxel plus cisplatin as front-line treatment of patients with advanced non-small-cell lung cancer: a randomized, multicenter phase III trial.* J Clin Oncol 2004 Jul 1;22(13):2602-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15226327>.

[Back to top](#)

## 2.25.5 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.26 Pancoast tumours

### Contents

- 1 What is the optimal management of Pancoast tumours?
  - 1.1 Introduction
- 2 Defining operable and inoperable disease in stage III
  - 2.1 Diagnostic work-up
  - 2.2 Treatment
    - 2.2.1 Resectable disease
    - 2.2.2 Unresectable disease
- 3 Evidence summary and recommendations
- 4 References
- 5 Appendices

### 2.26.1 What is the optimal management of Pancoast tumours?

#### 2.26.1.1 Introduction

The American College of Chest Physicians (ACCP) define a Pancoast tumour as a tumour which invades any of the structures at the apex of the chest, including the most superior ribs or periosteum, the lower nerve roots of the brachial plexus, the sympathetic chain near the apex of the chest or the subclavian vessels.<sup>[1]</sup>

The Pancoast syndrome occurs when the tumour invades the C8, T1-2 nerve roots and the sympathetic chain and consists of shoulder and arm pain, Horner's syndrome and weakness and atrophy of the small muscles of the hand.

The presence of Pancoast syndrome is not a prerequisite for a tumour to be defined as a Pancoast tumour.<sup>[1]</sup> Pancoast tumours account for less than 5% of lung malignancies. They are considered a distinct group because of their location in the lung apex where radical treatment options are challenging due to the surrounding clinically important major blood vessels and nerves and because of their unique clinical presentation.

#### 2.26.2 Defining operable and inoperable disease in stage III

The management of **Stage III NSCLC** has been divided into sections dependent on whether the disease is considered operable or inoperable at the time of diagnosis.

**Read full explanation**

[Back to top](#)

### 2.26.2.1 Diagnostic work-up

The aim of the diagnostic work-up is to determine whether the tumour can be resected with an acceptable complication rate and whether the patient is fit for surgical intervention.

In addition to the standard diagnostic tests of full blood count, biochemical evaluation, full respiratory function tests, computed tomography (CT scan) of chest and abdomen and positron emission tomography (PET) scan, magnetic resonance imaging (MRI) should be performed. An MRI is superior to CT in assessing structures of the thoracic inlet.<sup>[2]</sup>

Absolute and relative contra-indications to surgery based on preoperative imaging findings have been suggested.<sup>[3]</sup> Absolute contraindications include: distant metastases, N2 or N3 nodal disease, >50% vertebral body involvement, brachial plexus involvement above T1 nerve, and invasion of oesophagus/trachea. Relative contraindications to surgery include N1 or N3 nodal disease, invasion of the subclavian artery, <50% vertebral body involvement, intraforaminal extension, invasion of the common carotid or vertebral artery.

[Back to top](#)

### 2.26.2.2 Treatment

No Phase III study has addressed the optimal management of Pancoast tumour.

#### 2.26.2.2.1 Resectable disease

In patients deemed technically and medically fit for surgical resection, pre-operative concurrent chemoradiation followed by surgery is currently recommended as the standard treatment option for patients with Pancoast tumours.

This recommendation is based on the results of two Phase II studies conducted in a group of highly selected patients. In the North American intergroup 0160/Southwest Oncology Group (SWOG) 9416, 111 patients with T3-T4 N0-N1 tumours were treated with preoperative cisplatin and etoposide and concurrent radiation to 45Gy in 25 fractions. Following restaging at two to four weeks, patients with stable or responsive disease underwent thoracotomy. All patients were to receive an additional two cycles of chemotherapy. With this approach 75% (83 of 111) patients completed the entire treatment regimen. A complete resection (R0) was possible in 75 patients (90%) and gross total resection (R0 or R1) in 76 patients (92%). A five-year survival of 44% was reported for the entire group and for cases in which a complete response was achieved, the five-year survival was 54%. The authors reported these results were achieved with acceptable morbidity and mortality. The mortality rate was 2.7%.<sup>[4]</sup> There was no information on quality of life.

In the Japan Clinical Oncology Group (JCOG) 9806 Phase II trial, 76 patients received a regimen of two cycles of chemotherapy (mitomycin, vindesine and cisplatin) with concurrent radiation (45Gy/25f in a split-course) followed by surgical resection. Fifty-seven (76%) patients completed the regimen and a pathologic complete resection (R0) was achieved in 51 patients (68%). The five-year disease-free and overall survival rates were 45% and 56% respectively.<sup>[5]</sup> The mortality rate was 1.2% and quality of life was not addressed.

The results achieved with trimodality therapy reported in these Phase II trials appear superior to results achieved with single modality (radiation therapy alone) or bimodality therapy (radiation followed by surgery) reported in historical series. Radiotherapy alone was reported to achieve palliation of pain in 75% of patients<sup>[6]</sup> but longterm survival remained poor with five-year survival figures of 5 -23%.<sup>[7]</sup> A review of 23 studies employing bimodality therapy of radiation followed by surgical resection demonstrated a mean five-year survival of 36.5%.<sup>[7]</sup> Local relapse was reported in 40% of patients undergoing bimodality therapy.<sup>[8]</sup> It must be remembered that many of these studies did not include highly selected patients, were conducted before CT and MRI were available and used outdated radiotherapy techniques by today's standards.

The optimal regimen for preoperative therapy has not been established. There are concerns that the radiation dose employed in the Phase II preoperative chemoradiotherapy regimens is relatively low. This is of importance because, if an incomplete resection were performed, adjuvant radiation therapy would be offered. Thus the total radiation dose would be delivered in a split-course fashion which may allow tumour repopulation to occur resulting in suboptimal local control.<sup>[9]</sup> More intensive preoperative regimens using doses approaching 60Gy<sup>[10]</sup><sup>[11]</sup> or hyperfractionated accelerated radiation therapy<sup>[12]</sup> have been evaluated in single institution series and found to be feasible and tolerable. A regimen of accelerated radiotherapy (66Gy in 24 fractions, 2.75Gy/f given over 32 days, using concomitant boost) and concurrent daily cisplatin 6mg/m<sup>2</sup> followed by surgical resection has been employed in the Netherlands<sup>[13][14]</sup> The pathological complete response rate was 53% and the two and five-year overall survival was 74% and 33% respectively but severe late toxicity was seen in three long-term (>5 years) survivors.

No studies have determined whether, in cancers deemed resectable at diagnosis, preoperative chemoradiation therapy is superior to surgical resection followed by postoperative chemoradiation.

The results of a single institution prospective Phase II trial of surgery followed by concurrent chemoradiation therapy for Pancoast tumours have been reported.<sup>[15]</sup> Thirty-two patients with resectable or marginally resectable tumours treated at the MD Anderson Cancer Centre underwent segmentectomy or lobectomy with en bloc resection of the involved chest wall and complete nodal staging. Radiation therapy to a dose 60Gy in 50 twice daily fractions of 1.2Gy if margins were negative, and 64.8Gy in 54 twice daily fractions of 1.2Gy if margins were positive, commenced 14 to 42 days post surgery and was given concurrently with two cycles of cisplatin and etoposide. The protocol completion rate was 78%. Gross total resection was achieved in all patients. The five year DFS and OS were 45% and 50% respectively. The authors concluded that surgery followed by postoperative chemoradiation is safe and effective treatment for marginally resectable superior sulcus tumours.

[Back to top](#)

### **2.26.2.2.2 Unresectable disease**

There are no data on how patients who are fit for radical treatment, but have unresectable disease, should be managed. Extrapolation from the data for locally advanced non-Pancoast stage III NSCLC suggests that the concurrent administration of chemotherapy and radiotherapy is the optimal treatment approach (see What is the recommended treatment approach for the definitive management of patients with good performance status and inoperable Stage III disease?)<sup>[16]</sup>

A regimen of accelerated radiotherapy (66Gy in 24 fractions, 2.75Gy/f given over 32 days, using concomitant boost) and concurrent daily cisplatin 6mg/m<sup>2</sup> has been employed in the Netherlands.<sup>[13][14]</sup> The five-year locoregional disease-free survival was 48% and the two and five-year overall survival was 31% and 18% respectively.

For patients who are not fit for radical treatment, radiotherapy alone can offer palliation of pain.<sup>[6]</sup>

[Back to top](#)

### 2.26.3 Evidence summary and recommendations

Evidence summary	Level	References
No Phase III study has addressed the optimal management of Pancoast tumour		
For Pancoast tumours deemed to be resectable, 2 Phase II studies of trimodality therapy (concurrent chemoradiotherapy followed by surgery) have demonstrated superior results to those reported in historical series of single modality or bimodality therapy.	III-3, IV	[5], [4]
The optimal regimen for preoperative chemoradiotherapy has not been established.		
No studies have determined whether preoperative chemoradiation therapy is superior to surgical resection followed by postoperative chemoradiation.		

Evidence-based recommendation	Grade
In patients deemed technically and medically fit for surgical resection, pre-operative concurrent chemoradiation followed by surgery is an acceptable treatment option for patients with Pancoast tumours.	<b>C</b>

Evidence summary	Level	References
For Pancoast tumours deemed to be unresectable or in patients deemed not fit for surgery, treatment with concurrent chemotherapy and radiotherapy is recommended.	I	[16]

Evidence-based recommendation	Grade
For patients with good performance status and inoperable stage III NSCLC, the concurrent administration of chemotherapy and radiotherapy is recommended.	<b>A</b>

Evidence summary	Level	References
Radiation therapy alone can be used to palliate symptoms in patients with poor performance status or distant metastases.	IV	[6]

Evidence-based recommendation	Grade
For patients who have a poor performance status or distant metastatic disease, radiation therapy can be used to palliate symptoms due to Pancoast tumour.	<b>C</b>

Back to top

## 2.26.4 References

1. ↑ <sup>1.0 1.1</sup> Shen KR, Meyers BF, Lerner JM, Jones DR, American College of Chest Physicians. *Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition)*. Chest 2007 Sep;132(3 Suppl):290S-305S Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17873175>.
2. ↑ Heelan RT, Demas BE, Caravelli JF, Martini N, Bains MS, McCormack PM, et al. *Superior sulcus tumors: CT and MR imaging*. Radiology 1989 Mar;170(3 Pt 1):637-41 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2916014>.
3. ↑ Bruzzi JF, Komaki R, Walsh GL, Truong MT, Gladish GW, Munden RF, et al. *Imaging of non-small cell lung cancer of the superior sulcus: part 2: initial staging and assessment of resectability and therapeutic response*. Radiographics 2008;28(2):561-72 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18349458>.
4. ↑ <sup>4.0 4.1</sup> .
5. ↑ <sup>5.0 5.1</sup> .
6. ↑ <sup>6.0 6.1 6.2</sup> Van Houtte P, MacLennan I, Poulter C, Rubin P. *External radiation in the management of superior sulcus tumor*. Cancer 1984 Jul 15;54(2):223-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6202389>.
7. ↑ <sup>7.0 7.1</sup> Tamura M, Hoda MA, Klepetko W. *Current treatment paradigms of superior sulcus tumours*. Eur J Cardiothorac Surg 2009 Oct;36(4):747-53 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19699106>.
8. ↑ Rusch VW, Parekh KR, Leon L, Venkatraman E, Bains MS, Downey RJ, et al. *Factors determining outcome after surgical resection of T3 and T4 lung cancers of the superior sulcus*. J Thorac Cardiovasc Surg 2000 Jun;119(6):1147-53 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10838531>.
9. ↑ Mantell BS. *Superior sulcus (Pancoast) tumours: results of radiotherapy*. Br J Dis Chest 1973 Oct;67(4):315-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/4131847>.

10. ↑ Kwong KF, Edelman MJ, Suntharalingam M, Cooper LB, Gamliel Z, Burrows W, et al. *High-dose radiotherapy in trimodality treatment of Pancoast tumors results in high pathologic complete response rates and excellent long-term survival.* J Thorac Cardiovasc Surg 2005 Jun;129(6):1250-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15942564>.
11. ↑ Wright CD, Menard MT, Wain JC, Donahue DM, Grillo HC, Lynch TJ, et al. *Induction chemoradiation compared with induction radiation for lung cancer involving the superior sulcus.* Ann Thorac Surg 2002 May;73(5):1541-4 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12022546>.
12. ↑ Marra A, Eberhardt W, Pöttgen C, Theegarten D, Korfee S, Gauler T, et al. *Induction chemotherapy, concurrent chemoradiation and surgery for Pancoast tumour.* Eur Respir J 2007 Jan;29(1):117-26 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16971407>.
13. ↑ <sup>13.0</sup> <sup>13.1</sup> Kappers I, van Sandick JW, Burgers JA, Belderbos JS, Wouters MW, van Zandwijk N, et al. *Results of combined modality treatment in patients with non-small-cell lung cancer of the superior sulcus and the rationale for surgical resection.* Eur J Cardiothorac Surg 2009 Oct;36(4):741-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19699647>.
14. ↑ <sup>14.0</sup> <sup>14.1</sup> Kappers I, Klomp HM, Koolen MG, Uitterhoeve LJ, Kloek JJ, Belderbos JS, et al. *Concurrent high-dose radiotherapy with low-dose chemotherapy in patients with non-small cell lung cancer of the superior sulcus.* Radiother Oncol 2011 Nov;101(2):278-83 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21723638>.
15. ↑ Gomez DR, Cox JD, Roth JA, Allen PK, Wei X, Mehran RJ, et al. *A prospective phase 2 study of surgery followed by chemotherapy and radiation for superior sulcus tumors.* Cancer 2011 Jun 28 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21713767>.
16. ↑ <sup>16.0</sup> <sup>16.1</sup> O'Rourke N, Roqué I Figuls M, Farré Bernadó N, Macbeth F. *Concurrent chemoradiotherapy in non-small cell lung cancer.* Cochrane Database Syst Rev 2010 Jun 16;(6):CD002140 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20556756>.

## 2.26.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search
View PICO				

[Back to top](#)



---

## 2.27 Adjuvant whole brain radiotherapy following resection or stereotactic radiosurgery to the brain metastasis

---

### Contents

- 1 What is the clinical benefit of adjuvant whole brain radiotherapy following resection or stereotactic radiosurgery to the brain metastasis(es)?
  - 1.1 Introduction
  - 1.2 Radiotherapy dose and fractionation for adjuvant whole brain radiotherapy
    - 1.2.1 Clinical benefit of adjuvant whole brain radiotherapy
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.27.1 What is the clinical benefit of adjuvant whole brain radiotherapy following resection or stereotactic radiosurgery to the brain metastasis (es)?

---

#### 2.27.1.1 Introduction

Patients with one to three brain metastases may undergo surgical resection or stereotactic radiosurgery for these. The question then is whether whole brain radiotherapy is necessary in this setting.

#### 2.27.1.2 Radiotherapy dose and fractionation for adjuvant whole brain radiotherapy

##### 2.27.1.2.1 Clinical benefit of adjuvant whole brain radiotherapy

Patchell et al randomised patients with a solitary brain metastasis which had been resected to observation or adjuvant whole brain radiotherapy (WBRT).<sup>[1]</sup> Patients with both active and stable systemic disease were included. The addition of whole brain radiotherapy significantly reduced brain recurrences from 70% to 18% and reduced death from neurological causes from 44% to 14%. However there was no significant difference in median survival (48 weeks WBRT arm versus 43 weeks observation arm) or time of functional independence (37 weeks WBRT arm versus 35 weeks observation arm).



Aoyama et al conducted a similar study randomising patients with one to four brain metastases to stereotactic radiosurgery (SRS) alone or stereotactic radiosurgery followed by whole brain radiotherapy.<sup>[2]</sup> They found no difference in survival (median 7.5 months WBRT arm versus 8 months SRS alone arm), performance status or neurological function. Adjuvant whole brain radiotherapy did reduce actuarial brain recurrences at 12 months from 64% to 42%.

The largest trial examining this question has been conducted by the EORTC in patients with one to three brain metastases and stable systemic disease.<sup>[3]</sup> 359 underwent either surgical resection or stereotactic radiosurgery and were randomised to adjuvant whole brain radiotherapy or observation. The primary endpoint of the trial, survival with functional independence was similar between the arms. The median time to WHO performance status 2 was 10 months in the observation arm and 9.5 months in the WBRT arm. Median survival was also similar being 10.9 months in the observation arm and 10.7 months in the WBRT arm. The addition of WBRT significantly reduced intracranial progression from 78% to 48% and neurological deaths from 44% to 28%.

The trials by Kocher and Aoyama used a dose of 30Gy in 10 fractions for adjuvant whole brain radiotherapy. This was associated with mild acute toxicity (13% brisk skin erythema or dry desquamation, 10% moderate to severe nausea or vomiting, 4% severe headache).<sup>[3]</sup> Late Grade 3 effects occurred in 2-22% and Grade 4 1-4% with no difference between the observation and WBRT arms in the EORCT study.<sup>[3]</sup> The WBRT dose was higher in the Patchell study (50.4Gy in 28 fractions) and toxicity was not reported.

[Back to top](#)

## 2.27.2 Evidence summary and recommendations

Evidence summary	Level	References
Adjuvant whole brain radiotherapy following surgical resection or radiosurgery for one to three brain metastases reduces brain recurrences and neurological deaths.	II	[1], [2], [3]
Adjuvant whole brain radiotherapy following surgical resection or radiosurgery for one to three brain metastases does not improve survival or patient functional status.	II	[1], [2], [3]

Evidence-based recommendation	Grade
Patients who undergo surgical resection or radiosurgery for 1-3 brain metastases should be referred for discussion regarding adjuvant whole brain radiotherapy.	<b>B</b>

### Practice point

For patients undergoing adjuvant whole brain radiotherapy following surgical resection or stereotactic radiotherapy, the recommended dose of adjuvant whole brain radiotherapy is 30Gy in 10 fractions.

[Back to top](#)

## 2.27.3 References

1. ↑ <sup>1.0 1.1 1.2</sup> Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. *Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial*. JAMA 1998 Nov 4;280 (17):1485-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9809728>.
2. ↑ <sup>2.0 2.1 2.2</sup> Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. *Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial*. JAMA 2006 Jun 7;295(21):2483-91 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16757720>.
3. ↑ <sup>3.0 3.1 3.2 3.3 3.4</sup> Kocher M, Soffiatti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. *Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study*. J Clin Oncol 2011 Jan 10;29(2):134-41 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21041710>.

[Back to top](#)

## 2.27.4 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.28 Resection of brain metastasis

### Contents

- 1 What is the clinical benefit of resection of brain metastasis?
  - 1.1 Introduction
  - 1.2 Clinical benefit of surgery plus WBRT compared to WBRT alone: Randomised controlled trials
  - 1.3 Clinical benefit of surgery plus WBRT compared to WBRT alone: Meta analysis
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.28.1 What is the clinical benefit of resection of brain metastasis?

#### 2.28.1.1 Introduction

Brain metastases manifest clinically approximately equally as multiple or single brain metastases.<sup>[1]</sup> The term “single brain metastasis” is more correctly used to describe an isolated brain metastasis found in a patient presenting with an inoperable lung cancer or from an uncontrolled primary tumour, whilst the term “solitary brain metastasis” is most correctly used when the brain metastasis is diagnosed after radical, potentially curative treatment and remains the only site of disease.<sup>[2]</sup>

After diagnosis of brain metastasis median survival is around one month. Survival may increase with the addition of corticosteroids to two months and with whole brain radiotherapy (WBRT) to three to six months.<sup>[1]</sup>

Most patients will not be suitable for surgery because of multiple lesions, a surgically inaccessible lesion location, active primary disease, or co-morbidity.

Up to 40% of patients with cancer are found at autopsy to harbor brain metastases<sup>[1]</sup> and around 40% of these are due to NSCLC<sup>[2]</sup>, but despite the prevalence of the problem the majority of studies are retrospective or at best prospective phase 2 trials and include various primary tumour origins.

These studies of cohorts undergoing surgery and WBRT (most often for a variety of histologies, and including single, solitary and multiple brain metastases) consistently identify improved survival (with apparent cure in 2.5 – 5%) based on the following prognostic factors:

1. Solitary brain metastasis;
2. Single brain metastasis and control of extra cranial disease;

3. Better performance status; and
4. Younger age.

It is impossible to determine from these retrospective or single arm prospective studies if improvements in survival are attributable to the addition of surgery to WBRT or rather simply selection bias.

Surgery offers an opportunity for histological confirmation (in approximately 30% of patients there is an unknown primary site) and molecular analysis, which is increasingly important not only to confirm metastatic malignancy (up to 11% may have alternate diagnosis on biopsy<sup>[3]</sup>) but also to guide choice of systemic chemotherapy or targeted therapy.

[Back to top](#)

### 2.28.1.2 Clinical benefit of surgery plus WBRT compared to WBRT alone: Randomised controlled trials

Only three randomised trials have addressed the issue of the addition of surgery to WBRT. <sup>[3][4][5][6]</sup> These randomised trials in turn have included a wide range of histologies of the primary tumour and included highly selected populations so as to make their conclusions applicable to only a specific subset of patients. Limitations in the general applicability of the outcomes also relate to the time frame (1985 - 1993) of the studies and therefore imaging, surgical and radio therapeutic methods that are no longer 'state of the art'.

Patchell et al<sup>[3]</sup> randomly assigned 48 patients at a single US center with single brain metastases from various primary sites (37 with NSCLC) to surgery plus 36Gy WBRT versus WBRT alone. Recurrence at original site (20% versus 50%, [p=0.02]); overall median survival (15 versus 40 weeks, [p=0.01]); and functional independence (8 versus 38 weeks, [p<0.005]) all favoured addition of surgery in a statistically and clinically significant manner. The only limitation to the quality of the study was that analysis was not undertaken on an 'intention to treat' basis i.e. six (11%) patients were excluded after initial biopsy.

Vecht et al<sup>[4][5]</sup> randomly assigned 63 patients at multiple institutions in the Netherlands with single brain metastases from various primary sites (33 with NSCLC) to surgery plus 40Gy WBRT versus WBRT alone. Overall median survival (6 vs. 10 months, [p=0.04]); and functional independent survival (FIS) (3.5 versus 7.5 months [p=0.06], reaching statistical significance in the stratum with stable extra cranial disease [p=0.01]) favoured addition of surgery in a clinically significant manner. Of note in the stratum with progressive extra cranial disease there was no significant difference in FIS and absolute values were similarly poor in each arm.

Mintz et al<sup>[6]</sup> randomly assigned 84 patients at multiple institutions in Canada with single brain metastases from various primary sites (45 with NSCLC) to surgery plus 30Gy WBRT versus WBRT alone. The study was powered to detect a 50% increase in overall survival with 80% chance. Overall median survival and QOL did not differ in a clinically or statistically significant manner between the groups.

[Back to top](#)

### 2.28.1.3 Clinical benefit of surgery plus WBRT compared to WBRT alone: Meta analysis

A meta analysis by Hart et al <sup>[1]</sup> identified the above 3 RCTs enrolling 195 patients in total. No significant difference in survival was found (HR = 0.72, 95% CI 0.34 to 1.55, P = 0.40). Reduction in the risk of death due to neurological cause with surgery and WBRT approached significance (RR = 0.68, 95% CI: 0.43 - 1.09, [P = 0.11]). The risk of adverse events was not statistically different between arms. The authors concluded that surgery and WBRT may reduce the proportion of deaths due to neurological cause and may improve FIS but not overall survival.

There was substantial heterogeneity between the trials (I<sup>2</sup> = 83%). Both trials that implied improved survival after surgery reported better survival in those undergoing surgery and WBRT whilst that implying equivalence of the treatments reported better survival in patients receiving only WBRT. Indeed the Mintz trial enrolled patients with poorer performance status and higher burden of extra cranial disease. It may be therefore that the youngest and fittest patients with control of their extra cranial disease benefit from resection as it is the intra cranial disease that will be their life limiting pathology and as such improved local control may prolong both their quantity and quality of life.

No randomised evidence is available to guide addition of surgery to WBRT in the case of multiple metastases.

[Back to top](#)

## 2.28.2 Evidence summary and recommendations

Evidence summary	Level	References
Cure is possible in only a very small percentage of patients with brain metastasis.	I, II	[1], [3], [4], [5]
Improvement in long-term survival in unselected patients based on the addition of surgery to WBRT is unlikely.	I, II	[1], [3], [4], [5]
Improvement in OS due to the addition of surgery to WBRT in individualised cases is most likely in younger patients with good performance status and solitary brain metastasis or single brain metastasis and control of extra cranial disease.	II	[3], [4], [5]
Addition of surgery to WBRT may reduce the proportion of deaths due to neurological cause and may improve Functionally Independent Survival	II	[3], [4]

Evidence-based recommendation	Grade
In the absence of impending neurological emergency or the requirement of histological confirmation, patients with brain metastases may be managed with WBRT alone.	<b>B</b>

Evidence-based recommendation	Grade
In younger patients, with good performance status and solitary brain metastasis or single brain metastasis and control of extra cranial disease, addition of surgery to WBRT is a reasonable approach.	<b>C</b>

Practice point
Surgery may control symptoms more quickly than WBRT and is reasonable in cases of impending neurological emergency.

Practice point
Surgery provides histological confirmation and is reasonable in cases where the aetiology of the brain lesions is in question or histological information is not available from the primary tumour.

Practice point
In cases of multiple metastases, addition of surgery to WBRT may be reasonable for rapid symptom control or for histological confirmation.

Practice point
In cases of multiple metastases, addition of surgery to WBRT may be reasonable in highly individualised cases with the goal of improvement in local control, overall survival or FIS. Stereotactic radiosurgery may be an alternative to surgery in these patients.

[Back to top](#)

## 2.28.3 References

1. ↑ <sup>1.0 1.1 1.2 1.3 1.4 1.5</sup> Hart MG, Grant R, Walker M, Dickinson H. *Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases*. Cochrane Database Syst Rev 2005 Jan 25;(1):CD003292 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15674905>.
2. ↑ <sup>2.0 2.1</sup> Fuentes R, Bonfill X, Exposito J.. *Surgery versus radiosurgery for patients with a solitary brain metastasis from non-small cell lung cancer*. Cochrane Database Syst Rev 2010 Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004840.pub2/pdf>.
3. ↑ <sup>3.0 3.1 3.2 3.3 3.4 3.5 3.6</sup> Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. *A randomized trial of surgery in the treatment of single metastases to the brain*. N Engl J Med 1990 Feb 22; 322(8):494-500 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2405271>.
4. ↑ <sup>4.0 4.1 4.2 4.3 4.4 4.5</sup> Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al. *Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery?* Ann Neurol 1993 Jun;33(6):583-90 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8498838>.
5. ↑ <sup>5.0 5.1 5.2 5.3 5.4</sup> Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH, et al. *The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age*. Int J Radiat Oncol Biol Phys 1994 Jul 1;29(4):711-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8040016>.
6. ↑ <sup>6.0 6.1</sup> Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, et al. *A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis*. Cancer 1996 Oct 1;78(7):1470-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8839553>.

[Back to top](#)

## 2.28.4 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

---

## 2.29 Resection of primary disease after complete resection of metastatic disease

---

### Contents

- 1 What is the clinical benefit of resection of primary disease after complete resection of metastatic disease?
  - 1.1 Introduction
  - 1.2 Case series: Resection of primary disease after complete resection of metastatic disease
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.29.1 What is the clinical benefit of resection of primary disease after complete resection of metastatic disease?

---

#### 2.29.1.1 Introduction

Improvements in both structural and metabolic imaging in recent years mean that once undetectable metastases may now be identified. This is a 'double edged sword'. Whilst clinicians may be encouraged to pursue an aggressive approach on the basis that widespread metastasis have not been identified (despite PET, MRI and high resolution CT scan), a more pessimistic view is that it is only the high sensitivity of the imaging that has detected a metastasis whilst it is still solitary and that this in turn represents the 'tip of an oncological iceberg' that would in past years have been detected only when protruding from the water and at multiple sites.

[Back to top](#)

#### 2.29.1.2 Case series: Resection of primary disease after complete resection of metastatic disease

Multiple case reports and retrospective case series have reported long term survival in highly selected patients with brain, adrenal, small bowel, spleen, lymph node, skeletal muscle, and bone metastases with 5 year survival ranging from approximately 5% - 30% after resection of both primary and metastatic sites.



The only published prospective phase II study was reported by Downey et al<sup>[1]</sup> and details the treatment of a heterogenous group of 23 patients between 1992 and 1997 at a single US centre with a solitary, synchronous, resectable metastasis (including brain, adrenal, bone, lung, spleen and colon), a T 1-3, N 0-2 NSCLC and good performance status and adequate cardio-respiratory reserve to allow lung resection. Treatment included induction chemotherapy with mitomycin, vinblastine and cisplatin, followed by restaging, resection of all sites of disease and adjuvant vinblastine and cisplatin. In the case of a brain metastasis it was resected prior to induction chemotherapy and whole brain irradiation administered at the discretion of the treating neurosurgeon.

The median survival for all patients entered into the study was 11 months. Actual five-year survival from time of thoracotomy was 8%.

The author concludes that induction chemotherapy; surgical resection of primary and metastatic sites; and adjuvant chemotherapy is so poorly tolerated and commonly associated with disease progression as to preclude its recommendation. Further, that retrospective series reporting superior survival epitomise selection bias with only those selected for and completing resection of both sites of disease finding their way into institutional databases subsequently searched to report retrospective experience. This fact is imperative to appreciate when counseling an individual patient with an isolated metastasis considering embarking on an aggressive approach with curative intent, as even the fittest patients screened and accepted onto a phase II protocol have a 4 – 8% chance of long term disease free survival.

[Back to top](#)

## 2.29.2 Evidence summary and recommendations

---

### Practice point

In highly selected patients with T1-3 N0-1 lung cancers with good performance status, adequate pulmonary reserve and solitary site of metastasis, it may be reasonable to consider resection of primary and metastatic sites.

### Practice point

It is advisable to consider only those patients who would require less than pneumonectomy and with T 1-3, N0-1 NSCLC for resection of primary and metastatic sites.

## 2.29.3 References

---

1. ↑ Downey RJ, Ng KK, Kris MG, Bains MS, Miller VA, Heelan R, et al. *A phase II trial of chemotherapy and surgery for non-small cell lung cancer patients with a synchronous solitary metastasis*. Lung Cancer 2002 Nov;38(2):193-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12399132>.

[Back to top](#)

## 2.29.4 Appendices

---

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.30 Radiotherapy

---

### Contents

- 1 What is the clinical benefit of radiotherapy to the lung primary in stage IV NSCLC?
  - 1.1 Palliative thoracic radiotherapy
    - 1.1.1 Introduction
  - 1.2 Radiotherapy fractionation scheme for palliative radiotherapy to the lung primary in stage IV NSCLC
    - 1.2.1 Clinical benefit of palliative radiotherapy
    - 1.2.2 Toxicity of radiotherapy
  - 1.3 Optimal timing of palliative radiotherapy to the primary lung cancer in stage IV NSCLC
    - 1.3.1 Timing of radiotherapy
    - 1.3.2 Endobronchial brachytherapy
- 2 Evidence summary and recommendations
- 3 References

## 2.30.1 What is the clinical benefit of radiotherapy to the lung primary in stage IV NSCLC?

### 2.30.1.1 Palliative thoracic radiotherapy

#### **2.30.1.1.1 Introduction**

The aim of palliative radiotherapy in stage IV Non-Small Cell Lung Cancer (NSCLC) is to alleviate symptoms and improve quality of life. This has to be balanced against toxicity and costs of treatment and the need to attend for treatment for a number of days to weeks.

The cost-utility of different fractionation schemes has been analysed using data from the study by Kramer et al which randomised patients between 30Gy in 10 fractions and 16Gy in 2 fractions.<sup>[1]</sup> The higher dose provided significantly greater Quality Adjusted Life Years (20 weeks versus 13 weeks) but at greater societal cost. However the cost utility ratio was estimated to be US\$40900 per QALY which is within the range of acceptable cost effectiveness for medical interventions.

[Back to top](#)

### 2.30.1.2 Radiotherapy fractionation scheme for palliative radiotherapy to the lung primary in stage IV NSCLC

#### **2.30.1.2.1 Clinical benefit of palliative radiotherapy**

Lester et al conducted a systematic review of 14 randomised controlled trials which randomised between different doses of palliative radiotherapy.<sup>[2]</sup> These trials were heterogeneous in terms of the performance status of the study population, tumour pathology (NSCLC, SCLC, no pathological diagnosis) and tumour stage (stage III, stage IV or patients who were deemed unsuitable for curative treatment). In the majority of trials the endpoint was symptomatic response although this was measured using different instruments and by patients and/or clinicians at various time points. A meta-analysis was not performed due to heterogeneity of study population and outcomes measured.

All studies showed an improvement in symptoms from lung cancer with no significant difference in palliative benefit between the different fractionation regimens. There was no difference in radiological response. Toxicity was mild overall but was greater in arms with higher radiotherapy dose. The three studies which examined quality of life showed mixed findings and no clear advantage to a particular radiotherapy dose. Four studies showed an improvement in survival with the higher radiation dose although the applicability of this to stage IV NSCLC is uncertain.

The main symptoms palliated by thoracic radiotherapy are cough, dyspnoea, chest pain and haemoptysis. Cough is improved in 20-65% of patients, dyspnoea in 40-55%, chest pain in 39-80% and haemoptysis in 39-95%.<sup>[3][4][5][6]</sup> The median duration of palliative benefit for cough is 56-78 days, chest pain 56-74 days and haemoptysis 64-146 days).<sup>[3][4]</sup> This duration of palliation equates to 50% or more of the patients remaining survival time.

None of the trials showed any superiority of a particular radiotherapy dose and fractionation in achieving symptomatic response.<sup>[2]</sup> A higher radiotherapy dose (30Gy/10 fractions) has been associated with a longer duration of response and a slower progression of symptoms.<sup>[7]</sup> There is greater improvement in quality of life with higher radiotherapy doses (20Gy/5 fractions).<sup>[8]</sup> Higher doses (20Gy/5 fractions, 30-39Gy/10-13 fractions) have also been associated with a two month improvement in median survival and a 5-9% increase in one year survival and 3% at two years.<sup>[2][5][8][7]</sup> This survival benefit is largely in those patients with stage III NSCLC and good performance status but Kramer et al also demonstrated this for patients with stage IV NSCLC and good performance status.

[Back to top](#)

### **2.30.1.2.2 Toxicity of radiotherapy**

Palliative thoracic radiotherapy may cause fatigue, oesophagitis and pneumonitis. Acute toxicity is generally mild and self limiting.<sup>[2]</sup> Higher radiotherapy doses have been associated with increased toxicity particularly oesophagitis which can occur in 40-56% of patients.<sup>[3][4]</sup> More recent trials have shown no difference in acute toxicity between lower and higher doses of radiotherapy.<sup>[8][7]</sup> Late toxicity is uncommon, however, radiation myelitis has been documented in up to 2.5% of patients receiving 17Gy/2 fractions and 39Gy/13 fractions.<sup>[3][4][5]</sup> This can be reduced by limiting the spinal cord dose to LQED2 of 48Gy.<sup>[9]</sup>

[Back to top](#)

## **2.30.1.3 Optimal timing of palliative radiotherapy to the primary lung cancer in stage IV NSCLC**

### **2.30.1.3.1 Timing of radiotherapy**

In patients with minimal thoracic symptoms there is no advantage to immediate radiotherapy. A randomised trial of immediate versus delayed radiotherapy in these patients demonstrated that the chance of being alive and without moderate symptoms at six months was the same regardless of whether initial radiotherapy was given or not.<sup>[10]</sup> Only 42% of patients who did not receive initial radiotherapy, required it later for symptoms. There was no difference in psychological distress between the two patient groups.

[Back to top](#)

### 2.30.1.3.2 Endobronchial brachytherapy

Conventional external beam radiotherapy is delivered by a linear accelerator. An alternative way of delivering radiotherapy is via a catheter placed endobronchially at the site of the cancer. A radioactive seed travels through this catheter and releases radiation in close proximity to the cancer without the need to travel through healthy normal tissue. However the range of radiation delivered is small, in the order of 1-2cm, and this technique is not suitable for large extra-bronchial tumours.

Cardona systematically reviewed trials 13 randomised controlled trials comparing endobronchial brachytherapy to external beam radiotherapy and other interventions such as chemotherapy and laser.<sup>[11]</sup> These trials had small study populations and were heterogeneous with regard to the range of radiotherapy doses and other treatment modalities. They found that external beam radiotherapy had greater palliative efficacy compared with brachytherapy alone. There was no evidence to support a combination of external beam radiotherapy and brachytherapy over external beam radiotherapy alone. Endobronchial brachytherapy should be reserved for select patients who have previously been treated with external beam radiotherapy and have symptomatic recurrent central endobronchial tumour.

[Back to top](#)

## 2.30.2 Evidence summary and recommendations

Evidence summary	Level	References
Palliative thoracic radiotherapy can relieve symptoms due to primary lung cancer.	I	[2]
Lower doses of radiotherapy (10Gy/1 fraction, 17Gy/2 fractions) are equivalent to higher doses (20Gy/5 fractions, 30-39Gy/10-13 fractions and higher) in terms of symptom palliation.	I	[2]
In patients with good performance status, higher doses of radiotherapy (20Gy/5 fractions, 30-39Gy/10-13 fractions) give a modest survival benefit of approximately 5% at one year and 3% at two years and are associated with longer duration of symptom palliation.	I, II	[2], [7]
Acute toxicity of palliative thoracic radiotherapy is generally mild. Higher doses of radiotherapy are associated with greater acute toxicity particularly oesophagitis.	I	[2]
Patients with minimal thoracic symptoms do not benefit from immediate thoracic radiotherapy.	II	[10]
External beam radiotherapy is more effective for palliation of thoracic symptoms than endobronchial brachytherapy. There is no therapeutic advantage in giving both these treatment modalities over external beam radiotherapy alone.	I	[11]

Evidence-based recommendation	Grade
Patients who have thoracic symptoms of moderate severity from their primary lung cancer should be offered a course of palliative external beam thoracic radiotherapy.	<b>A</b>

Evidence-based recommendation	Grade
Patients who are of poor performance status should be treated with lower doses of palliative thoracic radiotherapy (8-10Gy/1 fraction, 16-17Gy/2 fractions) as this provides equivalent symptomatic response to higher doses of radiotherapy (20Gy/5 fraction, 30-39Gy in 10-13 fractions).	<b>A</b>

Evidence-based recommendation	Grade
Patients who are of good performance status should be treated with higher doses (20Gy/5 fractions, 30-39Gy/10-13 fractions) of palliative thoracic radiotherapy in order to maximise duration of palliation and survival.	<b>B</b>

Back to top

### 2.30.3 References

- ↑ van den Hout WB, Kramer GW, Noordijk EM, Leer JW. *Cost-utility analysis of short- versus long-course palliative radiotherapy in patients with non-small-cell lung cancer*. J Natl Cancer Inst 2006 Dec 20;98(24):1786-94 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17179480>.
- ↑ <sup>2.0 2.1 2.2 2.3 2.4 2.5 2.6 2.7</sup> Lester JF, Macbeth FR, Toy E, Coles B. *Palliative radiotherapy regimens for non-small cell lung cancer*. Cochrane Database Syst Rev 2006 Oct 18;(4):CD002143 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17054152>.
- ↑ <sup>3.0 3.1 3.2 3.3</sup> Medical Research Council Lung Cancer Working Party.. *Inoperable non-small-cell lung cancer (NSCLC): a Medical Research Council randomised trial of palliative radiotherapy with two fractions or ten fractions. Report to the Medical Research Council by its Lung Cancer Working Party*. Br J Cancer 1991;63(2):265-270. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1705140>.
- ↑ <sup>4.0 4.1 4.2 4.3</sup> Medical Research Council Lung Cancer Working Party.. *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. Medical Research Council Lung Cancer Working Party*. Br J Cancer 1992;65(6):934-941. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1377484>.

5. ↑ <sup>5.0 5.1 5.2</sup> Macbeth FR, Bolger JJ, Hopwood P, Bleeheh NM, Cartmell J, Girling DJ, et al. *Randomized trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Medical Research Council Lung Cancer Working Party.* Clin Oncol (R Coll Radiol) 1996;8(3):167-75 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8814371>.
6. ↑ .
7. ↑ <sup>7.0 7.1 7.2 7.3</sup> .
8. ↑ <sup>8.0 8.1 8.2</sup> .
9. ↑ Macbeth FR, Wheldon TE, Girling DJ, Stephens RJ, Machin D, Bleeheh NM, et al. *Radiation myelopathy: estimates of risk in 1048 patients in three randomized trials of palliative radiotherapy for non-small cell lung cancer. The Medical Research Council Lung Cancer Working Party.* Clin Oncol (R Coll Radiol) 1996;8(3):176-81 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8814372>.
10. ↑ <sup>10.0 10.1</sup> .
11. ↑ <sup>11.0 11.1</sup> Cardona AF, Reveiz L, Ospina EG, Ospina V, Yepes A. *Palliative endobronchial brachytherapy for non-small cell lung cancer.* Cochrane Database Syst Rev 2008 Apr 16;(2):CD004284 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18425900>.

Back to top

## 2.30.4 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

Back to top

## 2.31 Radiotherapy to the brain for patients with inoperable brain metastases

## Contents

- 1 What is the clinical benefit of radiotherapy to the brain for patients with inoperable brain metastases from NSCLC?
  - 1.1 Palliative whole brain radiotherapy
    - 1.1.1 Introduction
  - 1.2 Radiotherapy dose and fractionation for whole brain radiotherapy
    - 1.2.1 Clinical benefit of whole brain radiotherapy in patients with brain metastases
    - 1.2.2 Toxicity
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.31.1 What is the clinical benefit of radiotherapy to the brain for patients with inoperable brain metastases from NSCLC?

### 2.31.1.1 Palliative whole brain radiotherapy

#### 2.31.1.1.1 Introduction

The brain is a common site of relapse in NSCLC. The risk of developing brain metastases after surgery is 10% for stage I and II NSCLC.<sup>[1]</sup> Brain relapse is higher in stage III NSCLC ranging from 27%-55% after curative treatment.<sup>[2][3][4]</sup> Brain metastases are usually symptomatic with symptoms from surrounding oedema (headache, nausea, vomiting) and/or associated neurological deficits.

Important factors to consider when determining the management of patients with brain metastases are:

- Whether the metastases are solitary or multiple.
- Whether the primary and/or extra-cranial disease is controlled or uncontrolled.
- What the patient's performance status and neurological status is.
- Patient comorbidities that may impact on fitness for a particular treatment.

The RTOG has divided patients with brain metastases into three prognostic groups based on recursive partitioning analysis (RPA).<sup>[5]</sup>

- RPA Class I - Age <65, Karnofsky performance index  $\geq 70$ , controlled primary cancer, no extra-cranial metastases. Median survival 7.1 months.
- RPA Class II - All other patients not in Class I or II. Median survival 4.2 months.
- RPA Class III - Karnofsky performance status < 70. Median survival 2.3 months.

This prognostic grouping may help guide treatment recommendations.

[Back to top](#)



## 2.31.1.2 Radiotherapy dose and fractionation for whole brain radiotherapy

### **2.31.1.2.1 Clinical benefit of whole brain radiotherapy in patients with brain metastases**

Tsao et al conducted a systematic review of 30 randomised controlled trials of whole brain radiotherapy in 9415 participants.<sup>[6]</sup> These trials included patients with brain metastases from different primary cancers, although in the majority of trials over half the participants had lung cancer.

There was only one small trial of 48 participants which compared best supportive care with prednisone with radiotherapy.<sup>[7]</sup> There was no difference in improvement in performance status between the groups. Patients treated with radiotherapy had a median survival of 14 weeks compared with 10 weeks in the best supportive care arm. This trial was too small to draw any conclusions.

There have been many trials comparing different dose and fractionation schedules of radiotherapy.<sup>[6]</sup> Tsao et al found that compared with 30Gy in 10 fractions, higher doses and longer fractionation schemes resulted in similar survival at six months and similar improvements in neurological function.

Pease et al also conducted a systematic review which included non-randomised trials as well.<sup>[8]</sup> The median survival of patients undergoing radiotherapy was 3.2-5.8 months. Historical data shows a median survival of two to three months with best supportive care and steroids. They concluded that whole brain radiotherapy may have a survival gain of up to three months in patients of good performance status. This has to be interpreted with caution due to the non-randomised nature of the comparisons.

There have been many randomised trials of different radiotherapy dose and fractionation schemes for whole brain radiotherapy.<sup>[9][10][11][12][13][14]</sup> These trials are heterogenous in nature. Older studies included patients with symptoms of brain metastases and confirmation based on EEG or radioisotope brain scans rather than CT or MRI scans which have been used in contemporary studies. 56-80% of patients in these studies had metastatic lung cancer. Trials included patients with both solitary and multiple brain metastases. The patients had a range of performance status and neurological function.

The largest randomised trial was performed by the RTOG.<sup>[9]</sup> Patients were divided patients according to their neurological function (NF). NF I patients had minor neurological findings and could function normally, NF II patients were able to carry out normal activities with minimal difficulties, NF III patients were seriously limited in performing normal activities, required nursing care or hospitalisation, and were confined to a bed or wheelchair and NF IV patients required hospitalisation, constant nursing care and may have been unable to communicate or in a coma. Overall, neurological function improved in 47-52% of cases. Lung cancer patients who were NF II showed improvement in 37-38% of cases, and those in NF III improved in 66-72% of cases. The median time to neurological improvement was three weeks for NF II and one to two weeks for NF III patients. The median duration of response for all patients was 10-12 weeks. Median survival was 15-18 weeks. With respect to all outcome measures there was no advantage to doses higher than 20Gy in 5 fractions.

Other authors have examined a more favourable subgroup of patients by limiting trial entry to those with good performance status, good neurological function and/or controlled primary cancer or no extra-cranial metastases.<sup>[15][11][12][13][14]</sup> Gelber evaluated the outcomes of favourable patients (ambulatory, with absent primary or no

extracranial metastases) in the RTOG trial. These patients had a median survival of 25 weeks compared with 12 weeks for other patients, however there was no effect of radiotherapy fractionation on survival. They recommended 20Gy in 5 fractions for these patients. Other trials have used 30Gy in 10 fractions as a standard arm and have shown no improvement in outcomes with higher doses of radiotherapy.<sup>[11][12][14]</sup> Priestman compared 30Gy in 10 fractions with 12Gy in 2 fractions and found that median survival was better in the 30Gy arm (median 77d vs 84d, p=0.04).<sup>[13]</sup>

The response of specific symptoms to radiotherapy was headache 82-98%, nausea and vomiting 77--100%, motor loss 61-78%, impaired cognitive function 53-87%, cerebellar dysfunction 64-75%, cranial nerve palsy 59-71%, sensory loss 77%, cerebellar symptoms 59-77% and convulsions 76-95%.<sup>[9][13][11]</sup> The percentage of survival time spent in an improved or stable neurological state was 69-75% for ambulatory patients and 82-86% for non-ambulatory patients.<sup>[9]</sup>

[Back to top](#)

### 2.31.1.2.2 Toxicity

Toxicity was poorly reported in most trials. Many patients develop temporary alopecia.<sup>[13]</sup> Acute and late Grade 2 toxicities are seen in approximately 20 % of patients. Severe toxicities (Grade 3 and higher) are seen in 2% of cases, both in the acute and late setting.<sup>[14]</sup>

[Back to top](#)

## 2.31.2 Evidence summary and recommendations

Evidence summary	Level	References
Whole brain radiotherapy can palliate symptoms from brain metastases.	I	[6]
Dose fractionation regimens higher than 20Gy in 5 fractions or 30 Gy in 10 fractions are equivalent to these lower doses in terms of survival, palliation of symptoms and neurological function.	I, II	[6], [9]
Whole brain radiotherapy may improve survival in patients with good performance status compared with best supportive care and steroids.	III-3	[8]
Patient age, performance status and controlled primary tumour are strong prognostic factors for survival.	II	[5]

Evidence-based recommendation	Grade
Patients with brain metastases from lung cancer should be considered for whole brain radiotherapy.	<b>A</b>

Evidence-based recommendation	Grade
For patients with multiple metastases a dose of 20Gy in 5 fractions or 30Gy in 10 fractions is adequate for palliation of symptoms and improving neurological function.	<b>B</b>

Back to top

### 2.31.3 References

1. ↑ Hubbs JL, Boyd JA, Hollis D, Chino JP, Saynak M, Kelsey CR. *Factors associated with the development of brain metastases: analysis of 975 patients with early stage nonsmall cell lung cancer*. *Cancer* 2010 Nov 1; 116(21):5038-46 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20629035>.
2. ↑ Gaspar LE, Chansky K, Albain KS, Vallieres E, Rusch V, Crowley JJ, et al. *Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group*. *J Clin Oncol* 2005 May 1;23(13):2955-61 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15860851>.
3. ↑ Germain F, Wai ES, Berthelet E, Truong PT, Lesperance M. *Brain metastasis is an early manifestation of distant failure in stage III nonsmall cell lung cancer patients treated with radical chemoradiation therapy*. *Am J Clin Oncol* 2008 Dec;31(6):561-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19060588>.
4. ↑ Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. *Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain*. *Cancer* 2007 Apr 15;109(8):1668-75 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17342770>.
5. ↑ <sup>5.0 5.1</sup> Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. *Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials*. *Int J Radiat Oncol Biol Phys* 1997 Mar 1;37(4):745-51 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9128946>.
6. ↑ <sup>6.0 6.1 6.2 6.3</sup> Tsao MN, Lloyd N, Wong R, Chow E, Rakovitch E, Laperriere N. *Whole brain radiotherapy for the treatment of multiple brain metastases*. *Cochrane Database Syst Rev* 2006 Jul 19;3:CD003869 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16856022>.
7. ↑ Horton J, Baxter DH, Olson KB. *The management of metastases to the brain by irradiation and corticosteroids*. *Am J Roentgenol Radium Ther Nucl Med* 1971 Feb;111(2):334-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/5541678>.
8. ↑ <sup>8.0 8.1</sup> Pease NJ, Edwards A, Moss LJ. *Effectiveness of whole brain radiotherapy in the treatment of brain metastases: a systematic review*. *Palliat Med* 2005 Jun;19(4):288-99 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15984501>.
9. ↑ <sup>9.0 9.1 9.2 9.3 9.4</sup> Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al. *The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group*. *Int J Radiat Oncol Biol Phys* 1980 Jan;6(1):1-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6154024>.

10. ↑ Haie-Meder C, Pellae-Cosset B, Laplanche A, Lagrange JL, Tuchais C, Nogues C, et al. *Results of a randomized clinical trial comparing two radiation schedules in the palliative treatment of brain metastases*. *Radiother Oncol* 1993 Feb;26(2):111-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7681997>.
11. ↑ <sup>11.0 11.1 11.2 11.3</sup> Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. *The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group*. *Int J Radiat Oncol Biol Phys* 1981 Jul;7(7):891-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6171553>.
12. ↑ <sup>12.0 12.1 12.2</sup> Komarnicky LT, Phillips TL, Martz K, Asbell S, Isaacson S, Urtasun R. *A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916)*. *Int J Radiat Oncol Biol Phys* 1991 Jan;20(1):53-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1993631>.
13. ↑ <sup>13.0 13.1 13.2 13.3 13.4</sup> Priestman TJ, Dunn J, Brada M, Rampling R, Baker PG. *Final results of the Royal College of Radiologists' trial comparing two different radiotherapy schedules in the treatment of cerebral metastases*. *Clin Oncol (R Coll Radiol)* 1996;8(5):308-15 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8934050>.
14. ↑ <sup>14.0 14.1 14.2 14.3</sup> Murray KJ, Scott C, Greenberg HM, Emami B, Seider M, Vora NL, et al. *A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG) 9104*. *Int J Radiat Oncol Biol Phys* 1997 Oct 1;39(3):571-4 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9336134>.
15. ↑ Gelber RD, Larson M, Borgelt BB, Kramer S. *Equivalence of radiation schedules for the palliative treatment of brain metastases in patients with favorable prognosis*. *Cancer* 1981 Oct 15;48(8):1749-53 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6169424>.

[Back to top](#)

## 2.31.4 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.32 Stereotactic radiosurgery in the treatment of brain metastases

### Contents

- 1 What is the role of stereotactic radiosurgery in the treatment of brain metastases?
  - 1.1 Introduction
  - 1.2 SRS in addition to whole brain radiotherapy
  - 1.3 SRS as an alternative to surgical resection of brain metastasis
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.32.1 What is the role of stereotactic radiosurgery in the treatment of brain metastases?

#### 2.32.1.1 Introduction

Stereotactic radiosurgery (SRS) refers to the use of highly conformal radiotherapy delivered with the aid of a stereotactic head frame for precise tumour localisation. This extremely focussed radiotherapy allows a high radiation dose to be delivered to the tumour whilst minimising radiation to surrounding normal tissues.

[Back to top](#)

#### 2.32.1.2 SRS in addition to whole brain radiotherapy

An RTOG trial has evaluated the role of additional SRS to whole brain radiotherapy (WBRT) in patients with one to three unresectable brain metastases and stable systemic disease,<sup>[1]</sup> where 333 patients were treated with WBRT and then randomised to observation or SRS boost. Patients in the SRS arm had significantly reduced steroid use and improvement in performance status at six months compared with the observation group. Overall there was no difference in mean survival (5.7 months in observation arm versus 6.5 months in SRS arm). SRS boost was associated with a significant mean survival benefit in patients with a solitary metastasis (from 4.9 to 6.5 months), RPA Class I and metastases greater than 2cm. However, on multivariate analysis SRS boost was associated with improved local control but not survival. There was no difference in neurological deaths. These findings are supported by a small randomised trial reported by Kondziolka et al.<sup>[2]</sup>

The dose of SRS used in the RTOG trial was 24Gy for metastases measuring up to 2cm, 18Gy for 3-4cm and 15Gy for 3-4cm in size. The dose of WBRT was 37.5Gy in 15 fractions. There was no significant difference in acute or late toxicities between the arms (Grade 3 and 4 toxicity 3% in SRS arm versus 0% in observation arm, Grade 3 and 4 late toxicity 6% SRS arm versus 3% observation arm).

[Back to top](#)

### 2.32.1.3 SRS as an alternative to surgical resection of brain metastasis

Fuentes et al conducted a systematic review of this topic in patients with solitary brain metastases.<sup>[3]</sup> They could not show any advantage of one treatment over the other due to lack of randomised evidence.

There is one small randomised trial of SRS versus surgery in the treatment of brain metastases. Roos et al randomised patients with a solitary brain metastasis seen on MRI to SRS + WBRT versus surgery + WBRT . This trial was ceased early due to poor accrual and only 21 patients were randomised. There were no differences in brain relapse, overall survival or quality of life. (Roos 2011) There are single institution retrospective cohort studies which have compared surgery to SRS.<sup>[4][5][6][7][8]</sup> All of these are subject to bias due to factors determining selection for a particular treatment. Four of the five studies showed similar survival between the two treatments,<sup>[4][5][6][7]</sup> and three showed better local control with SRS.<sup>[5][6][7]</sup>

Auchter et al performed a retrospective multicentre study on patients with a solitary metastasis who would have met the eligibility criteria for that Patchell trial of surgical resection.<sup>[9][10]</sup> Patients could have active or stable systemic disease. All patients received WBRT and SRS boost. The median survival was 56 weeks, and for lung cancer 47 weeks. The median duration of functional independence was 44 weeks. There were no treatment related deaths. These results are not inferior to that reported in randomised trials of surgery in addition to WBRT. <sup>[10][11][12]</sup>

[Back to top](#)

## 2.32.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients with one to three unresectable brain metastases who have stable systemic disease, the addition of a stereotactic radiosurgery boost to whole brain radiotherapy improves local control and patient performance status and reduces steroid use.	II	[1]
In patients with one to three brain metastases who have stable systemic disease, the addition of a stereotactic radiosurgery boost to whole brain radiotherapy does not improve survival.	II	[1]
There is no evidence to suggest an advantage or disadvantage for stereotactic radiosurgery over surgery for the treatment of one to three metastases.	III-2	[5], [6], [4]

Evidence-based recommendation	Grade
Patients with one to three unresectable brain metastases and stable systemic disease may be considered for a stereotactic radiosurgery boost in addition to whole brain radiotherapy.	<b>C</b>

Evidence-based recommendation	Grade
Radiosurgery may be used as an alternative to surgery for patients with one to three brain metastases and stable systemic disease.	<b>C</b>

Back to top

## 2.32.3 References

- ↑ <sup>1.0 1.1 1.2</sup> Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. *Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial*. *Lancet* 2004 May 22;363(9422):1665-72 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15158627>.
- ↑ Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. *Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases*. *Int J Radiat Oncol Biol Phys* 1999 Sep 1;45(2):427-34 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10487566>.
- ↑ Fuentes R, Bonfill X, Exposito J.. *Surgery versus radiosurgery for patients with a solitary brain metastasis from non-small cell lung cancer*. *Cochrane Database Syst Rev* 2010 Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004840.pub2/pdf>.
- ↑ <sup>4.0 4.1 4.2</sup> Garell PC, Hitchon PW, Wen BC, Mellenberg DE, Torner J.. *Stereotactic radiosurgery versus microsurgical resection for the initial treatment of metastatic cancer to the brain*. *J Radiosurg* 1999;2(1):1-5.
- ↑ <sup>5.0 5.1 5.2 5.3</sup> Schöggel A, Kitz K, Reddy M, Wolfsberger S, Schneider B, Dieckmann K, et al. *Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases*. *Acta Neurochir (Wien)* 2000;142(6):621-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10949435>.
- ↑ <sup>6.0 6.1 6.2 6.3</sup> Rades D, Kueter JD, Veninga T, Gliemroth J, Schild SE. *Whole brain radiotherapy plus stereotactic radiosurgery (WBRT+SR5) versus surgery plus whole brain radiotherapy (OP+WBRT) for 1-3 brain metastases: results of a matched pair analysis*. *Eur J Cancer* 2009 Feb;45(3):400-4 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19062269>.
- ↑ <sup>7.0 7.1 7.2</sup> O'Neill BP, Iturria NJ, Link MJ, Pollock BE, Ballman KV, O'Fallon JR. *A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases*. *Int J Radiat Oncol Biol Phys* 2003 Apr 1;55(5):1169-76 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12654423>.



8. ↑ Bindal AK, Bindal RK, Hess KR, Shiu A, Hassenbusch SJ, Shi WM, et al. *Surgery versus radiosurgery in the treatment of brain metastasis*. J Neurosurg 1996 May;84(5):748-54 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8622147>.
9. ↑ Auchter RM, Lamond JP, Alexander E, Buatti JM, Chappell R, Friedman WA, et al. *A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis*. Int J Radiat Oncol Biol Phys 1996 Apr 1;35(1):27-35 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8641923>.
10. ↑ <sup>10.0</sup> <sup>10.1</sup> Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. *A randomized trial of surgery in the treatment of single metastases to the brain*. N Engl J Med 1990 Feb 22;322(8):494-500 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2405271>.
11. ↑ Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, et al. *A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis*. Cancer 1996 Oct 1;78(7):1470-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8839553>.
12. ↑ Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al. *Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery?* Ann Neurol 1993 Jun;33(6):583-90 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8498838>.

[Back to top](#)

## 2.32.4 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.33 Radiotherapy to the bone metastatic disease

### Contents

- 1 What is the clinical benefit of radiotherapy to the bone for metastatic disease from NSCLC?
  - 1.1 Introduction



1.2 Radiotherapy dose and fractionation for palliative radiotherapy to bony metastases
1.2.1 Clinical benefit of palliative radiotherapy
1.2.2 Toxicity
1.2.3 Adjuvant radiotherapy
2 Evidence summary and recommendations
3 References
4 Appendices

## 2.33.1 What is the clinical benefit of radiotherapy to the bone for metastatic disease from NSCLC?

### 2.33.1.1 Introduction

Bone metastases are a common site of metastasis from lung cancer. Pain is a presenting symptom in many cases.<sup>[1]</sup> Other potential complications include pathologic fracture, nerve root compression or spinal cord compression.

Cost-effectiveness studies of randomised controlled trials from the Netherlands,<sup>[2][3]</sup> USA<sup>[4]</sup> and Australia<sup>[5]</sup> also show a cost saving for single fraction radiotherapy, even when accounting for the higher rate of retreatment. Kanski et al<sup>[4]</sup> calculated an incremental cost effectiveness ratio US\$6973/QALY when comparing 8Gy in 1 fraction to 30Gy in 10 fraction. Australian data show a cost saving of between AU\$795 - \$1468 for single fraction radiotherapy compared to five fractions.<sup>[5]</sup>

[Back to top](#)

### 2.33.1.2 Radiotherapy dose and fractionation for palliative radiotherapy to bony metastases

#### 2.33.1.2.1 Clinical benefit of palliative radiotherapy

There are no randomised trials of radiotherapy compared to best supportive care and analgesia alone. However many trials of radiotherapy fractionation in patients with painful bony metastases (not at risk of pathological fracture) show a clear palliative benefit from radiotherapy.<sup>[6][7][8]</sup>

There have been three contemporary meta-analyses comparing the effect of single fraction radiotherapy (commonly 8Gy) to fractionated regimens (commonly 20-25Gy/5 fractions, 24Gy/6 fractions, 30Gy/10 fractions).<sup>[6][7][8]</sup> These included bony metastases from all primary sites. Response was measured using a number of different scales but essentially was pain reduction by at least one category or 50%. All meta-analyses have shown no difference in pain response by radiotherapy fractionation. Higher biological doses are not associated with greater pain relief.<sup>[8]</sup>

The most recent meta-analysis of 5000 patients showed an overall response rate of 58% with single fraction and 59% with fractionated radiotherapy.<sup>[6]</sup> Complete response rates were 23% and 24% respectively. Single fraction was associated with a slightly higher rate of pathologic fracture (3.2% versus 2.8%) and spinal cord compression (2.8% versus 1.9%) but this was not statistically significant. Retreatment however, was significantly greater in the single fraction arm, 20% versus 8%.

Steenland et al performed the largest randomised trial of radiotherapy in patients with bony metastases. 1171 patients were randomised to 8Gy in 1 fraction or 24Gy in 6 fractions.<sup>[2]</sup> 25% of patients had lung cancer. Response was defined as a reduction of 2 points from the initial pain score. Overall response rates were 71% for single fraction and 73% for fractionated radiotherapy and complete response rates were 14% in each arm.<sup>[2][9]</sup> Patients receiving single fraction were significantly more likely to receive retreatment (25% versus 7%) and sustain a pathological fracture (4% versus 2%).

In lung cancer, the overall response rate for pain was 58% for single fraction and 62% for multiple fractions. The mean time to response was three weeks and mean duration of response was 11 weeks in lung cancer. Retreatment in lung cancer patients was 32% for the single fraction arm and 5% for the fractionated arm.

The majority of trials have included patients with painful bony metastases. There is one trial that specifically recruited patients with neuropathic pain from bony metastases and showed similar efficacy between 8Gy in 1 fraction and 20Gy in 5 fractions.<sup>[10]</sup> There was no difference in the incidence of spinal cord or cauda equina compression.

[Back to top](#)

### **2.33.1.2.2 Toxicity**

There is no difference in acute toxicity or quality of life between single fraction and fractionated radiotherapy treatment for painful bony metastases.<sup>[6][8][2]</sup>

[Back to top](#)

### **2.33.1.2.3 Adjuvant radiotherapy**

There are no prospective trials that have evaluated the role of adjuvant radiotherapy following surgery for fixation of a pathological or impending pathological fracture. Townsend et al<sup>[11]</sup> performed a retrospective analysis of 64 orthopaedic procedures where surgery alone was performed in 29 and adjuvant radiotherapy was given in 35. The median dose was 30Gy in 10 fractions. The proportion of patients who were ambulant at any time post-operatively was 53% in the radiation group compared with 12% in the surgery only group. The need for a second orthopaedic procedure to the same site was reduced from 15% to 3%. On multivariate analysis, adjuvant radiotherapy was the only prognostic factor for improved functional status after surgery.

The trials of radiotherapy fractionation are not necessarily applicable to the post-operative setting. If bone healing is the endpoint, a multifraction schedule (30Gy in 10 fractions) has been shown to have significantly higher rates of recalcification than single fraction (8Gy in 1 fraction).<sup>[12]</sup>

[Back to top](#)

## 2.33.2 Evidence summary and recommendations

Evidence summary	Level	References
Palliative radiotherapy can relieve pain from bony metastases.	I	[6], [7], [8]
A single 8Gy fraction of radiotherapy provides equivalent pain relief to a fractionated course of radiotherapy to higher doses.	I	[6], [7], [8]
A single 8Gy fraction of radiotherapy is associated with higher rates of radiotherapy retreatment.	I	[6], [7], [8]
A single 8Gy fraction of radiotherapy is associated with higher rates of pathological fracture, although the absolute difference is less than 1-2%.	I, II	[6], [2]
There is no difference in toxicity and quality of life between single fraction radiotherapy and a fractionated course	I, II	[6], [2]
Adjuvant radiotherapy after fixation of a pathological fracture can improve functional status.	III-3	[11]

Evidence-based recommendation	Grade
Patients who have pain from bony metastases (not at risk of pathological fracture) should be offered palliative radiotherapy.	<b>A</b>

Evidence-based recommendation	Grade
A single fraction of 8Gy is recommended if the clinical endpoint is pain relief.	<b>A</b>

Evidence-based recommendation	Grade
Patients who have had orthopaedic fixation of a pathological fracture may be considered for adjuvant radiotherapy.	<b>C</b>

[Back to top](#)

## 2.33.3 References

1. ↑ .

2. ↑ <sup>2.0 2.1 2.2 2.3 2.4 2.5</sup> Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, et al. *The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study*. *Radiother Oncol* 1999 Aug;52(2):101-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10577695>.
3. ↑ van den Hout WB, van der Linden YM, Steenland E, Wiggeraad RG, Kievit J, de Haes H, et al. *Single-versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial*. *J Natl Cancer Inst* 2003 Feb 5;95(3):222-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12569144>.
4. ↑ <sup>4.0 4.1</sup> Kanski A, James J, Hartsell W, Leibenhaut MH, Janjan N, Curran W, et al. *Economic analysis of radiation therapy oncology group 97-14: multiple versus single fraction radiation treatment of patients with bone metastases*. *Am J Clin Oncol* 2009 Aug;32(4):423-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19546803>.
5. ↑ <sup>5.0 5.1</sup> Pollicino CA, Turner SL, Roos DE, O'Brien PC. *Costing the components of pain management: analysis of Trans-Tasman Radiation Oncology Group trial (TROG 96.05): one versus five fractions for neuropathic bone pain*. *Radiother Oncol* 2005 Sep;76(3):264-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16153729>.
6. ↑ <sup>6.0 6.1 6.2 6.3 6.4 6.5 6.6 6.7 6.8</sup> Chow E, Harris K, Fan G, Tsao M, Sze WM. *Palliative radiotherapy trials for bone metastases: a systematic review*. *J Clin Oncol* 2007 Apr 10;25(11):1423-36 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17416863>.
7. ↑ <sup>7.0 7.1 7.2 7.3 7.4</sup> Sze WM, Shelley M, Held I, Mason M. *Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy - a systematic review of the randomised trials*. *Cochrane Database Syst Rev* 2004;(2):CD004721 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15106258>.
8. ↑ <sup>8.0 8.1 8.2 8.3 8.4 8.5 8.6</sup> Wu JS, Wong R, Johnston M, Bezjak A, Whelan T, Cancer Care Ontario Practice Guidelines Initiative Supportive Care Group. *Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases*. *Int J Radiat Oncol Biol Phys* 2003 Mar 1;55(3):594-605 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12573746>.
9. ↑ van der Linden YM, Lok JJ, Steenland E, Martijn H, van Houwelingen H, Marijnen CA, et al. *Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment*. *Int J Radiat Oncol Biol Phys* 2004 Jun 1;59(2):528-37 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15145173>.
10. ↑ Roos DE, Turner SL, O'Brien PC, Smith JG, Spry NA, Burmeister BH, et al. *Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05)*. *Radiother Oncol* 2005 Apr;75(1):54-63 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15878101>.
11. ↑ <sup>11.0 11.1</sup> Townsend PW, Rosenthal HG, Smalley SR, Cozad SC, Hassanein RE. *Impact of postoperative radiation therapy and other perioperative factors on outcome after orthopedic stabilization of impending or pathologic fractures due to metastatic disease*. *J Clin Oncol* 1994 Nov;12(11):2345-50 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7669102>.
12. ↑ Koswig S, Budach V. *Remineralization and pain relief in bone metastases after after different radiotherapy fractions (10 times 3 Gy vs. 1 time 8 Gy). A prospective study*. *Strahlenther Onkol* 1999 Oct;175(10):500-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10554645>.

Back to top

## 2.33.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.34 Radiotherapy in metastatic spinal cord compression

---

### **Contents**

- 1 What is the clinical benefit of radiotherapy in metastatic spinal cord compression?
  - 1.1 Introduction
  - 1.2 Clinical benefit of palliative radiotherapy
  - 1.3 Toxicity
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.34.1 What is the clinical benefit of radiotherapy in metastatic spinal cord compression?

---

### 2.34.1.1 Introduction

Spinal cord compression occurs in 5-10% of patients with metastatic cancer. Patients can present with pain or neurological deficits such as limb weakness, sensory changes and bowel or bladder dysfunction. Urgent treatment is necessary to prevent progression of neurological deficit which may result in a reduction in functional status.

The diagnosis of spinal cord compression is ideally based on an MRI scan. However, clinical symptoms and signs together with consistent findings on a CT scan may be sufficient for diagnosis.

[Back to top](#)

### 2.34.1.2 Clinical benefit of palliative radiotherapy

The two treatment modalities used in the treatment of spinal cord compression are surgery and radiotherapy. There have been no randomised trials comparing the two single modalities.

Patchell (2005)<sup>[1]</sup> compared the addition of decompressive surgery to radiotherapy with radiotherapy alone in patients with single level spinal cord compression. These patients had <48 hours of paraplegia and an expected life expectancy of three months and included patients with an unstable spine (ie pathological fracture or bone in the spinal canal). One hundred and one patients were randomised to surgery and radiotherapy versus radiotherapy alone. The radiotherapy dose was 30Gy in 10 fractions for both arms. Functional outcomes were significantly better in the surgical arm with a post treatment ambulatory rate of 84% versus 57% and median duration of ambulation 122 days versus 13 days. Of the non-ambulant patients 62% of the surgical group and 19% of the radiotherapy alone group regained the ability to walk. Patients undergoing surgery also had better continence, muscle strength and reduced dexamethasone and analgesic use. However, 18/51 patients in the radiotherapy alone group had unstable spines, which radiotherapy alone would not be expected to fix and could explain the poorer outcomes in this group.

For patients treated with radiotherapy alone, there has been one randomised trial of different dose fractionation regimens.<sup>[2]</sup> Three hundred patients with an expected life expectancy greater than six months and no indication for surgery were randomised between 16Gy in 2 fractions and a split course of 15Gy in 3 fractions followed by 15Gy in 5 fractions. 28% of patients had NSCLC. There were no differences in outcomes between the two schedules. Reduction in pain was seen in 57% of patients, with 24% having a complete response and 33% partial response. Ninety percent of ambulant patients remained ambulant, 35% of non-ambulant patients became ambulant but no paraplegic patients regained the ability to walk. The median duration of improvement was 3.5 months and the median survival was four months.

An international multicentre retrospective study of 1034 patients with spinal cord compression<sup>[3]</sup> compared different radiotherapy fractionation schemes ie 8Gy in 1 fraction, 20Gy in 5 fractions, 30Gy in 10 fractions, 37.5 Gy in 15 fractions and 40Gy in 20 fractions). Fourteen percent of patients had NSCLC. There were no differences in functional outcomes between the radiation regimens. Motor function improved in 26%-31% and post-treatment ambulatory rates ranged from 63-74%. Infield recurrences at two years were higher in the 8 and 20Gy arms compared to the other doses (24-26% versus 7-14%).

Short course radiotherapy (8Gy in 1 fraction, 20Gy in 5 fractions) has been compared to long course radiotherapy (30Gy in 10 fractions, 35.5Gy in 15 fractions, 40Gy in 20 fractions) in patients with spinal cord compression from NSCLC.<sup>[3]</sup> In this retrospective study of 252 patients there was no difference seen in motor function between the groups. Motor function improved in 13% versus 15%, was unchanged in 53% versus 55% and deteriorated in 34% versus 30% in the long course versus short course arms respectively. Median survival was four months.

[Back to top](#)

### 2.34.1.3 Toxicity

The toxicity from these radiotherapy regimens is mild. In the only prospective study to report toxicity there was 1% Gd 3 oesophagitis, 0.5% Gd 3 pharyngeal dysphagia and 3% Gd 3 vomiting.<sup>[2]</sup>

[Back to top](#)

## 2.34.2 Evidence summary and recommendations

Evidence summary	Level	References
Palliative radiotherapy can relieve pain and improve neurological function in patients with spinal cord compression from metastatic cancer.	II	[2], [1]
For patients treated with radiotherapy alone, lower radiotherapy doses (8Gy/1 fraction, 16Gy/2 fraction, 20Gy/5 fractions) have equivalent ambulatory and functional outcomes compared with higher radiotherapy doses.	II, III-2	[2], [3]
Decompressive surgery in addition to radiotherapy may improve ambulatory and functional outcomes in selected patients with single level spinal cord compression.	II	[1]

Evidence-based recommendation	Grade
Patients who have spinal cord compression from metastatic cancer should be considered for radiotherapy, either as primary treatment or following surgery.	<b>B</b>

Evidence-based recommendation	Grade
Recommended radiotherapy doses for patients treated with radiotherapy alone are 8Gy-20Gy in 1- 5 fractions.	<b>B</b>

Practice point
Patients with spinal cord compression may be commenced on dexamethasone 4-16mg a day to reduce oedema around the spinal cord. This can be weaned once treatment is complete.

Back to top

### 2.34.3 References

1. ↑ <sup>1.0 1.1 1.2</sup> Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. *Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial.* Lancet ;366(9486):643-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16112300>.
2. ↑ <sup>2.0 2.1 2.2 2.3</sup> Maranzano E, Bellavita R, Rossi R, De Angelis V, Frattegiani A, Bagnoli R, et al. *Short-course versus split-course radiotherapy in metastatic spinal cord compression: results of a phase III, randomized, multicenter trial.* J Clin Oncol 2005 May 20;23(15):3358-65 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15738534>.
3. ↑ <sup>3.0 3.1 3.2</sup> Rades D, Stalpers LJ, Schulte R, Veninga T, Basic H, Engenhardt-Cabilic R, et al. *Defining the appropriate radiotherapy regimen for metastatic spinal cord compression in non-small cell lung cancer patients.* Eur J Cancer 2006 May;42(8):1052-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16580192>.

Back to top



## 2.34.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.35 First-line chemotherapy

---

### 2.35.1 What is the optimal first-line chemotherapy regimen in patients with stage IV inoperable NSCLC?

---

### 2.35.2 Evidence summary and recommendations

---

[Back to top](#)

### 2.35.3 References

---

[Back to top](#)

## 2.36 Carboplatin vs cisplatin

---

### 2.36.1 Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC?

---

#### 2.36.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.36.3 References

---

[Back to top](#)

## 2.37 Optimal new agent or platinum combination regimen

---

### 2.37.1 Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC?

---

#### 2.37.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.37.3 References

---

[Back to top](#)

## 2.38 Monotherapy with new 3G agent vs platinum combination therapy

---

### 2.38.1 Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC?

---

#### 2.38.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.38.3 References

---

[Back to top](#)

## 2.39 Three vs two chemotherapy agents

---

### 2.39.1 Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC?

---

#### 2.39.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.39.3 References

---

[Back to top](#)

## 2.40 Non-platinum doublet vs platinum doublet regimen

---

### 2.40.1 Are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens for treatment of stage IV inoperable NSCLC?

---

#### 2.40.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.40.3 References

---

[Back to top](#)

## 2.41 Optimal duration of first-line chemotherapy

---

### 2.41.1 What is the optimal duration of first-line chemotherapy for treatment of stage IV inoperable NSCLC?

---

#### 2.41.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.41.3 References

---

[Back to top](#)

## 2.42 Chemotherapy with biologic or targeted therapy vs chemotherapy alone

---

### 2.42.1 Is chemotherapy with a biologic or targeted therapy superior to chemotherapy alone in unselected patients for treatment of stage IV inoperable NSCLC?

---

#### 2.42.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.42.3 References

---

[Back to top](#)

## 2.43 Optimal chemotherapy for overall QoL

---

### 2.43.1 What is the optimal chemotherapy regimen for overall quality of life for patients in the treatment of stage IV inoperable NSCLC?

---

#### 2.43.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.43.3 References

---

[Back to top](#)

## 2.44 Optimal first-line maintenance therapy

---

### 2.44.1 What is the optimal first-line maintenance therapy for treatment of stage IV inoperable NSCLC?

---

#### 2.44.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.44.3 References

---

[Back to top](#)

## 2.45 Optimal second-line therapy

---

### 2.45.1 How effective is monotherapy compared with combination therapy as second-line therapy in patients with stage IV inoperable NSCLC?

---

#### 2.45.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.45.3 References

---

[Back to top](#)

## 2.46 Optimal third-line therapy in unselected patients

---

### 2.46.1 What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC?

---

#### 2.46.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.46.3 References

---

[Back to top](#)

## 2.47 Optimal systemic therapy regimen - poor performance status

---

### 2.47.1 What is the optimal systemic therapy regimen for patients with poor performance status for treatment of stage IV inoperable NSCLC?

---

#### 2.47.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.47.3 References

---

[Back to top](#)

## 2.48 Optimal systemic therapy regimen for elderly patients

---

## 2.48.1 What is the optimal systemic therapy regimen for elderly patients for treatment of stage IV inoperable NSCLC?

---

### 2.48.2 Evidence summary and recommendations

---

[Back to top](#)

### 2.48.3 References

---

[Back to top](#)

## 2.49 Optimal systemic therapy regimen in selected patients

---

### 2.49.1 What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC?

---

#### 2.49.2 Evidence summary and recommendations

---

[Back to top](#)

#### 2.49.3 References

---

[Back to top](#)

## 2.50 Optimal systemic therapy and duration

---

### **Contents**

- 1 What is the optimal systemic therapy and duration to be used for the treatment of limited stage small cell lung cancer?
- 2 Evidence summary and recommendations
- 3 References



## 2.50.1 What is the optimal systemic therapy and duration to be used for the treatment of limited stage small cell lung cancer?

Meta-analyses have demonstrated that platinum based regimens are associated with greater response rates but differing toxicity profiles relative to non-platinum regimens in patients with limited stage disease.<sup>[1][2]</sup>

The latter may represent alternative therapy, however, their role in chemoradiation for limited stage disease has not been assessed. In this regard the platinum-etoposide regimen is considered the standard chemotherapy backbone for patients with limited stage small cell lung cancer.

The evidence for the benefit of consolidation or maintenance therapy post response to induction therapy is controversial with conflicting results from phase III trials<sup>[3][4][5]</sup> and meta-analyses.<sup>[6]</sup>

[Back to top](#)

## 2.50.2 Evidence summary and recommendations

Evidence summary	Level	References
Platinum-Etoposide regimens remain the gold standard chemotherapy in patients with limited stage small cell lung cancer, particularly where concurrent radiation therapy is deemed appropriate	I	[1], [2]
Maintenance or consolidation therapy post response to initial beyond four cycles of chemotherapy.	I, II	[6], [2], [3]

Evidence-based recommendation	Grade
Platinum-etoposide regimens are considered the standard systemic chemotherapy in the treatment of limited stage small cell lung cancer.	<b>B</b>

Evidence-based recommendation	Grade
Therapy beyond the standard four cycles of induction chemotherapy cannot be recommended.	<b>A</b>

### Practice point

It is advisable to use platinum plus etoposide for four cycles in patients with limited stage small cell lung cancer.

[Back to top](#)

## 2.50.3 References

1. ↑ <sup>1.0</sup> <sup>1.1</sup> Amarasena IU, Walters JA, Wood-Baker R, Fong K. *Platinum versus non-platinum chemotherapy regimens for small cell lung cancer*. Cochrane Database Syst Rev 2008 Oct 8;(4):CD006849 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18843733>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> <sup>2.2</sup> Rossi A, Garassino MC, Cinquini M, Sburlati P, Di Maio M, Farina G, et al. *Maintenance or consolidation therapy in small-cell lung cancer: a systematic review and meta-analysis*. Lung Cancer 2010 Nov;70(2):119-28 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20188431>.
3. ↑ <sup>3.0</sup> <sup>3.1</sup> Lee SM, Woll PJ, Rudd R, Ferry D, O'Brien M, Middleton G, et al. *Anti-angiogenic therapy using thalidomide combined with chemotherapy in small cell lung cancer: a randomized, double-blind, placebo-controlled trial*. J Natl Cancer Inst 2009 Aug 5;101(15):1049-57 Available from: [HTTP://WWW.NCBI.NLM.NIH.GOV/PUBMED/19608997](http://WWW.NCBI.NLM.NIH.GOV/PUBMED/19608997).
4. ↑ Shepherd FA, Giaccone G, Seymour L, Debruyne C, Bezjak A, Hirsh V, et al. *Prospective, randomized, double-blind, placebo-controlled trial of marimastat after response to first-line chemotherapy in patients with small-cell lung cancer: a trial of the National Cancer Institute of Canada-Clinical Trials Group and the European Organization for Research and Treatment of Cancer*. J Clin Oncol 2002 Nov 15;20(22):4434-9 Available from: [HTTP://WWW.NCBI.NLM.NIH.GOV/PUBMED/12431965](http://WWW.NCBI.NLM.NIH.GOV/PUBMED/12431965).
5. ↑ Giaccone G, Debruyne C, Felip E, Chapman PB, Grant SC, Millward M, et al. *Phase III study of adjuvant vaccination with BCG/bacille Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971-08971B; Silva Study)*. J Clin Oncol 2005 Oct 1;23(28):6854-64 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16192577>.
6. ↑ <sup>6.0</sup> <sup>6.1</sup> Bozcuk H, Artac M, Ozdogan M, Savas B. *Does maintenance/consolidation chemotherapy have a role in the management of small cell lung cancer (SCLC)? A metaanalysis of the published controlled trials*. Cancer 2005 Dec 15;104(12):2650-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16284984>.

[Back to top](#)

## 2.50.4 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.51 Optimal concurrent chemotherapy

---

### Contents

- 1 What is the optimal concurrent chemotherapy to be used for the treatment of limited stage small cell lung cancer with radiotherapy?
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.51.1 What is the optimal concurrent chemotherapy to be used for the treatment of limited stage small cell lung cancer with radiotherapy?

---

One phase III trial had demonstrated that the standard three-weekly cisplatin + etoposide regimen was superior to the daily administration of cisplatin plus etoposide in terms of local control and patient tolerance.<sup>[1]</sup>

Two phase II trials had demonstrated that the addition of a third agent to the cisplatin-etoposide regimen during radiation therapy provided no additional benefit. Prolonged oral etoposide administration provided no added benefit.<sup>[2][3]</sup> Hence three-weekly cisplatin etoposide is considered as standard of care with chest radiation therapy.

Meta-analysis has demonstrated that survival time in patients with limited stage disease correlated with the shorter time from the first day of chemotherapy to the last day of chest radiation therapy, supporting prior phase III trials demonstrating the advantage of early versus late chemoradiotherapy.<sup>[4]</sup>

Back to top

## 2.51.2 Evidence summary and recommendations

Evidence summary	Level	References
Standard three-weekly cisplatin plus etoposide regimen is superior to the daily administration of cisplatin plus etoposide, in terms of local control and patient tolerance.	II, IV	[1], [2], [3]

Evidence-based recommendation	Grade
Platinum plus etoposide is recommended as the chemotherapy backbone for concurrent chemoradiotherapy in patients with limited stage small cell lung cancer.	<b>B</b>

Practice point
<p>It is advisable to use three-weekly platinum and etoposide chemotherapy during concurrent chemoradiotherapy for limited stage small cell lung cancer.</p> <p>Chest irradiation is optimally commenced early during the course of chemotherapy.</p>

Back to top

## 2.51.3 References

- ↑ <sup>1.0</sup> <sup>1.1</sup> Sculier JP, Lafitte JJ, Efremidis A, Florin MC, Lecomte J, Berchier MC, et al. *A phase III randomised study of concomitant induction radiochemotherapy testing two modalities of radiosensitisation by cisplatin (standard versus daily) for limited small-cell lung cancer.* Ann Oncol 2008 Oct;19(10):1691-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18504252>.

2. ↑ <sup>2.0</sup> <sup>2.1</sup> Horn L, Bernardo P, Sandler A, Wagner H, Levitan N, Levitt ML, et al. *A phase II study of paclitaxel + etoposide + cisplatin + concurrent radiation therapy for previously untreated limited stage small cell lung cancer (E2596): a trial of the Eastern Cooperative Oncology Group.* J Thorac Oncol 2009 Apr;4(4):527-33 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19240650>.
3. ↑ <sup>3.0</sup> <sup>3.1</sup> Lee SH, Ahn YC, Kim HJ, Lim DH, Lee SI, Nam E, et al. *Early concurrent chemoradiotherapy with prolonged oral etoposide and cisplatin for limited-stage small-cell lung cancer.* Jpn J Clin Oncol 2003 Dec; 33(12):620-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14769839>.
4. ↑ De Ruyscher D, Pijls-Johannesma M, Bentzen SM, Minken A, Wanders R, Lutgens L, et al. *Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer.* J Clin Oncol 2006 Mar 1;24(7):1057-63 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16505424>.

[Back to top](#)

## 2.51.4 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.52 Optimal dose and fractionation schedule of prophylactic cranial irradiation

### Contents

- 1 What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with limited stage SCLC?
- 2 Evidence summary and recommendations
- 3 References

## 2.52.1 What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with limited stage SCLC?

The Prophylactic Cranial Irradiation Overview Collaborative Group meta-analysis of individual patient data from seven trials confirmed a reduction in the incidence of brain metastases with increasing doses of prophylactic cranial irradiation (PCI), but no effect on survival.<sup>[1]</sup>

A randomised intergroup trial directly compared standard dose to higher dose PCI in patients with limited stage small cell lung cancer and a CR to initial therapy.<sup>[2]</sup> The standard dose arm received 25Gy in 10 daily fractions. The higher dose arm received either 36Gy in 18 daily fractions, or 36Gy in twice daily fractions of 1.5Gy each as part of a RTOG sub study. Higher doses of PCI conferred neither an increase in survival nor a reduction in the incidence of subsequent brain metastases. Nor was there any advantage to hyperfractionation in terms of neurotoxicity or QOL in the RTOG sub study of 265 patients.<sup>[3]</sup> In that sub study, patients receiving 36Gy had a significantly higher incidence of neurological deterioration and toxicity (as per the study's definition of these endpoints) than those receiving 25Gy. Quality of life and neurotoxicity were also reported for the entire patient cohort of 720 patients.<sup>[4]</sup> In this larger analysis, there were no differences in QOL or neurotoxicity observed between the different dose arms.

[Back to top](#)

## 2.52.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients with limited stage small cell lung cancer achieving a CR to initial therapy, prophylactic cranial irradiation doses greater than 25Gy in 10 fractions confer no clinically significant advantage.	I, II	[1], [2]

Evidence-based recommendation	Grade
Patients with limited stage small cell lung cancer achieving a complete response to initial therapy should receive prophylactic cranial irradiation to a dose of 25Gy in 10 daily fractions.	<b>B</b>

[Back to top](#)

### 2.52.3 References

1. ↑ <sup>1.0</sup> <sup>1.1</sup> Prophylactic Cranial Irradiation Overview Collaborative Group. *Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission (review)*. Cochrane Database Syst Rev 2009 Jan Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002805/pdf>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> Le P  choux C, Dunant A, Senan S, Wolfson A, Quoix E, Faivre-Finn C, et al. *Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial*. *Lancet Oncol* 2009 May;10(5):467-74 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19386548>.
3. ↑ Wolfson AH, Bae K, Komaki R, Meyers C, Movsas B, Le Pechoux C, et al. *Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer*. *Int J Radiat Oncol Biol Phys* 2011 Sep 1;81(1):77-84 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20800380>.
4. ↑ Le P  choux C, Laplanche A, Faivre-Finn C, Ciuleanu T, Wanders R, Lerouge D, et al. *Clinical neurological outcome and quality of life among patients with limited small-cell cancer treated with two different doses of prophylactic cranial irradiation in the intergroup phase III trial (PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01)*. *Ann Oncol* 2011 May;22(5):1154-63 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21139020>.

[Back to top](#)

### 2.52.4 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.53 Optimal treatment volume for thoracic radiotherapy?

### Contents

- 1 What is the optimal treatment volume in patients with limited stage SCLC receiving thoracic radiotherapy?
  - 1.1 Introduction
  - 1.2 Radiotherapy to pre- versus post-chemotherapy volume
  - 1.3 Elective nodal irradiation
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.53.1 What is the optimal treatment volume in patients with limited stage SCLC receiving thoracic radiotherapy?

---

### 2.53.1.1 Introduction

The addition of thoracic radiotherapy to chemotherapy improves survival for fit patients with LS SCLC.<sup>[1][2]</sup> The optimal radiotherapy treatment volume has however not yet been definitively elucidated. This is because no completed randomised trials have directly compared the inclusion versus omission of elective nodal volumes, and just a single trial has compared the inclusion of pre- vs. post-chemotherapy volumes in radiotherapy portals.

[Back to top](#)

### 2.53.1.2 Radiotherapy to pre- versus post-chemotherapy volume

In a randomised trial from 1987 Kies et al. reported no differences in relapse patterns or survival between patients receiving radiotherapy to pre-induction vs. post-induction chemotherapy tumour volumes.<sup>[3]</sup> In that trial, patients achieving a complete response to chemotherapy still received radiotherapy to mediastinal and ipsilateral hilar nodes. A recent trial examining the inclusion of pre- versus post-chemotherapy tumour extent reported an interim analysis also showing no significant difference in local control or survival between the two groups.<sup>[4]</sup> Since this was an interim report, the planned statistical power had not yet been achieved however. The North Central Cancer Treatment Group (NCCTG) performed a randomised trial of hyperfractionated versus split-course radiotherapy.<sup>[5]</sup> Radiotherapy in that trial encompassed only the post-chemotherapy disease extent. Never the less local failure outside the radiotherapy portals occurred in fewer than 7% of patients.

[Back to top](#)



### 2.53.1.3 Elective nodal irradiation

It should be noted that most randomised trials in LS SCLC incorporated elective nodal irradiation in their treatment protocols. No randomised trials have directly compared elective vs. involved nodal radiotherapy. However, several studies including phase II and phase III trials have reported outcomes for patients where radiotherapy was limited to involved nodal volumes only.<sup>[4][6][7][8][9][10][11][12][13]</sup> With the exception of one study<sup>[8]</sup> which reported an isolated nodal failure rate of 11%, all studies reported nodal failure rates well below 10%. Since toxicity, particularly oesophagitis is a significant problem with concurrent chemo-radiotherapy for SCLC, limiting radiotherapy portals to include only involved nodal regions is attractive.

[Back to top](#)

### 2.53.2 Evidence summary and recommendations

Evidence summary	Level	References
Delivery of thoracic radiotherapy to the post-chemotherapy extent of disease does not adversely affect local recurrence or overall survival.	II	[3], [4]
No mature high level evidence exists, however, available data suggests that the rates of isolated nodal failure are low using an involved field approach.	II, III-2, IV	[4], [7], [8], [9], [10], [11], [12], [13], [6]

Evidence-based recommendation	Grade
Where radiotherapy is delivered after chemotherapy has begun, radiotherapy target volumes should be based on the post-chemotherapy volume of disease. Radiotherapy should be delivered to all originally involved nodal regions irrespective of their response to chemotherapy.	<b>B</b>

Evidence-based recommendation	Grade
Elective nodal irradiation may be omitted to reduce toxicity.	<b>C</b>

### Practice point

In the setting of SCLC, positron emission tomography (PET) appears useful both for staging as well as for the definition of radiotherapy volumes. Where available, information from PET scans should be incorporated into radiotherapy target definition.

[Back to top](#)

## 2.53.3 References

1. ↑ Pignon JP, Arriagada R, Ihde DC, Johnson DH, Perry MC, Souhami RL, et al. *A meta-analysis of thoracic radiotherapy for small-cell lung cancer*. N Engl J Med 1992 Dec 3;327(23):1618-24 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1331787>.
2. ↑ Warde P, Payne D. *Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis*. J Clin Oncol 1992 Jun;10(6):890-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1316951>.
3. ↑ <sup>3.0</sup> <sup>3.1</sup> Kies MS, Mira JG, Crowley JJ, Chen TT, Pazdur R, Grozea PN, et al. *Multimodal therapy for limited small-cell lung cancer: a randomized study of induction combination chemotherapy with or without thoracic radiation in complete responders; and with wide-field versus reduced-field radiation in partial responders: a Southwest Oncology Group Study*. J Clin Oncol 1987 Apr;5(4):592-600 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3031226>.
4. ↑ <sup>4.0</sup> <sup>4.1</sup> <sup>4.2</sup> <sup>4.3</sup> Hu X, Bao Y, Zhang L, Guo Y, Chen YY, Li KX, et al. *Omitting elective nodal irradiation and irradiating postinduction versus preinduction chemotherapy tumor extent for limited-stage small cell lung cancer: Interim analysis of a prospective randomized noninferiority trial*. Cancer 2011 May 19 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21598237>.
5. ↑ Bonner JA, Sloan JA, Shanahan TG, Brooks BJ, Marks RS, Krook JE, et al. *Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma*. J Clin Oncol 1999 Sep;17(9):2681-91 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10561342>.
6. ↑ <sup>6.0</sup> <sup>6.1</sup> Xia B, Chen GY, Cai XW, Zhao JD, Yang HJ, Fan M, et al. *Is involved-field radiotherapy based on CT safe for patients with limited-stage small-cell lung cancer? Radiother Oncol* 2011 Nov 4 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22056536>.
7. ↑ <sup>7.0</sup> <sup>7.1</sup> van Loon J, De Ruyscher D, Wanders R, Boersma L, Simons J, Oellers M, et al. *Selective nodal irradiation on basis of (18)FDG-PET scans in limited-disease small-cell lung cancer: a prospective study*. Int J Radiat Oncol Biol Phys 2010 Jun 1;77(2):329-36 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19782478>.
8. ↑ <sup>8.0</sup> <sup>8.1</sup> <sup>8.2</sup> De Ruyscher D, Bremer RH, Koppe F, Wanders S, van Haren E, Hochstenbag M, et al. *Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: a phase II trial*. Radiother Oncol 2006 Sep;80(3):307-12 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16949169>.

9. ↑ <sup>9.0</sup> <sup>9.1</sup> Baas P, Belderbos JS, Senan S, Kwa HB, van Bochove A, van Tinteren H, et al. *Concurrent chemotherapy (carboplatin, paclitaxel, etoposide) and involved-field radiotherapy in limited stage small cell lung cancer: a Dutch multicenter phase II study*. Br J Cancer 2006 Mar 13;94(5):625-30 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16465191>.
10. ↑ <sup>10.0</sup> <sup>10.1</sup> Belderbos J, Baas P, Senan S. *Reply: Patterns of nodal recurrence after omission of elective nodal irradiation for limited-stage small-cell lung cancer*. BJC 2007;July 16; 97(2): 276. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2360309/>.
11. ↑ <sup>11.0</sup> <sup>11.1</sup> Shirvani SM, Komaki R, Heymach JV, Fossella FV, Chang JY. *Positron Emission Tomography /Computed Tomography-Guided Intensity-Modulated Radiotherapy for Limited-Stage Small-Cell Lung Cancer*. Int J Radiat Oncol Biol Phys 2011 Apr 12 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21489716>.
12. ↑ <sup>12.0</sup> <sup>12.1</sup> Colaco R, Sheikh H, Lorigan P, Blackhall F, Hulse P, Califano R, et al. *Omitting elective nodal irradiation during thoracic irradiation in limited-stage small cell lung cancer - Evidence from a phase II trial*. Lung Cancer 2011 Oct 17 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22014897>.
13. ↑ <sup>13.0</sup> <sup>13.1</sup> Watkins JM, Wahlquist AE, Zauls AJ, Shirai K, Garrett-Mayer E, Aguero EG, et al. *Involved-field radiotherapy with concurrent chemotherapy for limited-stage small-cell lung cancer: disease control, patterns of failure and survival*. J Med Imaging Radiat Oncol 2010 Oct;54(5):483-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20958948>.

[Back to top](#)

## 2.53.4 Appendices

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.54 Optimal 1st line chemotherapy regimen and duration

**Contents**

- 1 What is the optimal chemotherapy regimen and duration of therapy in extensive stage small cell lung cancer in the first-line setting?
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.54.1 What is the optimal chemotherapy regimen and duration of therapy in extensive stage small cell lung cancer in the first-line setting?

Based on the current evidence including randomised phase II;<sup>[1]</sup> and phase III trials;<sup>[2][3][4][5]</sup> platinum etoposide combination is still considered as the gold standard.

Based on phase III trials<sup>[6][7][8][9]</sup> and subsequent meta-analyses<sup>[10][11]</sup> Irinotecan combined with platinum may be as efficacious, with differing toxicity profiles. However, the data is heterogeneous and in some studies in favor of non-Caucasian population.

The utility of triplet combinations have provided no additional benefit based on phase II trials<sup>[12][13]</sup>

No studies have directly compared four versus six cycles of therapy in the first-line setting.

The use of maintenance or consolidation therapy after initial response to first-line therapy has not been shown to be of added benefit in terms of overall survival whether evaluating single agent cytotoxic agents such as Irinotecan or biologicals such as thalidomide or marimastat. This conclusion is based upon phase II,<sup>[14]</sup> and randomised phase III trials.<sup>[15][16]</sup>

[Back to top](#)

## 2.54.2 Evidence summary and recommendations

Evidence summary	Level	References
The platinum etoposide combination is still considered as the standard first-line regimen.	II	[1], [2], [3], [4], [5]
Irinotecan combined with platinum may be as efficacious as platinum etoposide in specific populations but with differing toxicity profiles.	I, II	[10], [11], [6], [7], [8], [9]
The utility of triplet combinations have provided no additional benefit.	II	[12], [13]

Evidence summary	Level	References
The use of maintenance or consolidation therapy after initial response to first-line therapy has not been shown to be of added benefit.	II	[14], [15], [16]

Evidence-based recommendation	Grade
The platinum etoposide regimen is recommended as the first-line therapy for patients with extensive stage small cell lung cancer. Irinotecan-platinum may be an alternative in selected patients.	<b>B</b>

Practice point
It is advisable to consider the platinum etoposide regimen as first-line therapy in patients with extensive stage small cell lung cancer, treatment should continue for at least four to six cycles. Maintenance therapy provides no additional benefit.

Back to top

### 2.54.3 References

1. ↑ <sup>1.0</sup> <sup>1.1</sup> Ettinger DS, Finkelstein DM, Ritch PS, Lincoln ST, Blum RH, Eastern Cooperative Oncology Group. *Study of either ifosfamide or teniposide compared to a standard chemotherapy for extensive disease small cell lung cancer: an Eastern Cooperative Oncology Group randomized study (E1588)*. Lung Cancer 2002 Sep;37(3):311-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12234701>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> Eckardt JR, von Pawel J, Papai Z, Tomova A, Tzekova V, Crofts TE, et al. *Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naïve patients with extensive-disease small-cell lung cancer*. J Clin Oncol 2006 May 1;24(13):2044-51 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16648504>.
3. ↑ <sup>3.0</sup> <sup>3.1</sup> Schmittel A, Sebastian M, Fischer von Weikersthal L, Martus P, Gauler TC, Kaufmann C, et al. *A German multicenter, randomized phase III trial comparing irinotecan-carboplatin with etoposide-carboplatin as first-line therapy for extensive-disease small-cell lung cancer*. Ann Oncol 2011 Aug;22(8):1798-804 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21266516>.
4. ↑ <sup>4.0</sup> <sup>4.1</sup> Sundstrøm S, Bremnes RM, Kaasa S, Aasebø U, Hatlevoll R, Dahle R, et al. *Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up*. J Clin Oncol 2002 Dec 15;20(24):4665-72 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12488411>.

5. ↑ <sup>5.0</sup> <sup>5.1</sup> Socinski MA, Smit EF, Lorigan P, Konduri K, Reck M, Szczesna A, et al. *Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naive patients with extensive-stage small-cell lung cancer.* J Clin Oncol 2009 Oct 1;27(28):4787-92 Available from: [HTTP://WWW.NCBI.NLM.NIH.GOV/PUBMED/19720897](http://www.ncbi.nlm.nih.gov/pubmed/19720897).
6. ↑ <sup>6.0</sup> <sup>6.1</sup> Hanna N, Bunn PA Jr, Langer C, Einhorn L, Guthrie T Jr, Beck T, et al. *Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer.* J Clin Oncol 2006 May 1;24(13):2038-43 Available from: [HTTP://WWW.NCBI.NLM.NIH.GOV/PUBMED/16648503](http://www.ncbi.nlm.nih.gov/pubmed/16648503).
7. ↑ <sup>7.0</sup> <sup>7.1</sup> Lara PN Jr, Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE, et al. *Phase III trial of irinotecan /cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124.* J Clin Oncol 2009 May 20;27(15):2530-5 Available from: [HTTP://WWW.NCBI.NLM.NIH.GOV/PUBMED/19349543](http://www.ncbi.nlm.nih.gov/pubmed/19349543).
8. ↑ <sup>8.0</sup> <sup>8.1</sup> Zatloukal P, Cardenal F, Szczesna A, Gorbunova V, Moiseyenko V, Zhang X, et al. *A multicenter international randomized phase III study comparing cisplatin in combination with irinotecan or etoposide in previously untreated small-cell lung cancer patients with extensive disease.* Ann Oncol 2010 Sep;21(9):1810-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20231298>.
9. ↑ <sup>9.0</sup> <sup>9.1</sup> Hermes A, Bergman B, Bremnes R, Ek L, Fluge S, Sederholm C, et al. *Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial.* J Clin Oncol 2008 Sep 10;26(26):4261-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18779613>.
10. ↑ <sup>10.0</sup> <sup>10.1</sup> Jiang J, Liang X, Zhou X, Huang L, Huang R, Chu Z, et al. *A meta-analysis of randomized controlled trials comparing irinotecan/platinum with etoposide/platinum in patients with previously untreated extensive-stage small cell lung cancer.* J Thorac Oncol 2010 Jun;5(6):867-73 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20521354>.
11. ↑ <sup>11.0</sup> <sup>11.1</sup> Lima JP, dos Santos LV, Sasse EC, Lima CS, Sasse AD. *Camptothecins compared with etoposide in combination with platinum analog in extensive stage small cell lung cancer: systematic review with meta-analysis.* J Thorac Oncol 2010 Dec;5(12):1986-93 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20978445>.
12. ↑ <sup>12.0</sup> <sup>12.1</sup> Greco FA, Thompson DS, Morrissey LH, Erland JB, Burris HA 3rd, Spigel DR, et al. *Paclitaxel /carboplatin/etoposide versus paclitaxel/topotecan for extensive-stage small cell lung cancer: a Minnie Pearl Cancer Research Network randomized, prospective phase II trial.* Oncologist 2005 Oct;10(9):728-33 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16249353>.
13. ↑ <sup>13.0</sup> <sup>13.1</sup> Leyvraz S, Pampallona S, Martinelli G, Ploner F, Perey L, Aversa S, et al. *A threefold dose intensity treatment with ifosfamide, carboplatin, and etoposide for patients with small cell lung cancer: a randomized trial.* J Natl Cancer Inst 2008 Apr 16;100(8):533-41 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18398095>.
14. ↑ <sup>14.0</sup> <sup>14.1</sup> Han JY, Kim HT, Lim KY, Yoon SJ, Lee DH, Lee JS. *Randomized phase II study of maintenance irinotecan therapy versus observation following induction chemotherapy with irinotecan and cisplatin in extensive disease small cell lung cancer.* J Thorac Oncol 2008 Sep;3(9):1039-45 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18758308>.

15. ↑ <sup>15.0</sup> <sup>15.1</sup> Hanna NH, Sandier AB, Loehrer PJ Sr, Ansari R, Jung SH, Lane K, et al. *Maintenance daily oral etoposide versus no further therapy following induction chemotherapy with etoposide plus ifosfamide plus cisplatin in extensive small-cell lung cancer: a Hoosier Oncology Group randomized study.* Ann Oncol 2002 Jan;13(1):95-102 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11863118>.
16. ↑ <sup>16.0</sup> <sup>16.1</sup> Lee SM, Woll PJ, Rudd R, Ferry D, O'Brien M, Middleton G, et al. *Anti-angiogenic therapy using thalidomide combined with chemotherapy in small cell lung cancer: a randomized, double-blind, placebo-controlled trial.* J Natl Cancer Inst 2009 Aug 5;101(15):1049-57 Available from: <HTTP://WWW.NCBI.NLM.NIH.GOV/PUBMED/19608997>.

[Back to top](#)

## 2.54.4 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.55 Optimal second-line therapy

### Contents

- 1 What is the optimal second-line therapy in patients with extensive stage small cell lung cancer?
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.55.1 What is the optimal second-line therapy in patients with extensive stage small cell lung cancer?

Based on meta-analyses<sup>[1][2]</sup> second line chemotherapy provides a survival benefit in particular patients who are chemotherapy responsive and who had progressed at least three months post first-line therapy.

Phase III trials have demonstrated equivalent efficacy of topotecan (oral or IV) or CAV. However topotecan is associated with greater treatment-related toxicity (grade 4 thrombocytopenia and grade 3/4 anaemia) and oral topotecan greater diarrhoea relative to the IV formulation.<sup>[3][1]</sup>

Amrubicin in a phase II trial has demonstrated superior response rate to topotecan in chemotherapy sensitive patients with less severe neutropenia.<sup>[4]</sup> Other agents including bortezomib,<sup>[5]</sup> histone deacetylase inhibitors,<sup>[6]</sup> and mTOR inhibitors,<sup>[7]</sup> evaluated in phase II trials have demonstrated no benefit.

[Back to top](#)

## 2.55.2 Evidence summary and recommendations

Evidence summary	Level	References
Second-line chemotherapy provides a survival benefit in particular patients who are chemotherapy responsive and who had progressed at least three months post first-line therapy.	I	[1], [2]
Topotecan (oral or IV) has equivalent efficacy relative to CAV, but differing toxicity profile. Patients treated with IV or oral topotecan suffered a reduced frequency of grade 4 neutropenia, but higher frequency of grade 4 thrombocytopenia and grade 3 /4 anaemia relative to CAV.	I, II	[3], [1]

Evidence-based recommendation	Grade
Topotecan or CAV are recommended as second-line therapy in patients with extensive stage small cell lung cancer who have chemotherapy responsive disease (i.e. relapse > three months post first-line therapy).	<b>A</b>

[Back to top](#)



### 2.55.3 References

---

1. ↑ <sup>1.0 1.1 1.2 1.3</sup> Cheng S, Evans WK, Stys-Norman D, Shepherd FA, Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. *Chemotherapy for relapsed small cell lung cancer: a systematic review and practice guideline*. J Thorac Oncol 2007 Apr;2(4):348-54 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17409809>.
2. ↑ <sup>2.0 2.1</sup> Pelayo Alvarez M, Gallego Rubio O, Bonfill Cosp X, Agra Varela Y. *Chemotherapy versus best supportive care for extensive small cell lung cancer*. Cochrane Database Syst Rev 2009 Oct 7;(4): CD001990 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19821287>.
3. ↑ <sup>3.0 3.1</sup> Eckardt JR, von Pawel J, Pujol JL, Papai Z, Quoix E, Ardizzoni A, et al. *Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer*. J Clin Oncol 2007 May 20;25(15):2086-92 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17513814>.
4. ↑ Jotte R, Conkling P, Reynolds C, Galsky MD, Klein L, Fitzgibbons JF, et al. *Randomized phase II trial of single-agent amrubicin or topotecan as second-line treatment in patients with small-cell lung cancer sensitive to first-line platinum-based chemotherapy*. J Clin Oncol 2011 Jan 20;29(3):287-93 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21135284>.
5. ↑ Lara PN Jr, Chansky K, Davies AM, Franklin WA, Gumerlock PH, Guaglianone PP, et al. *Bortezomib (PS-341) in relapsed or refractory extensive stage small cell lung cancer: a Southwest Oncology Group phase II trial (S0327)*. J Thorac Oncol 2006 Nov;1(9):996-1001 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17409985>.
6. ↑ Otterson GA, Hodgson L, Pang H, Vokes EE, Cancer and Leukemia Group B. *Phase II study of the histone deacetylase inhibitor Romidepsin in relapsed small cell lung cancer (Cancer and Leukemia Group B 30304)*. J Thorac Oncol 2010 Oct;5(10):1644-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20871263>.
7. ↑ Pandya KJ, Dahlberg S, Hidalgo M, Cohen RB, Lee MW, Schiller JH, et al. *A randomized, phase II trial of two dose levels of temsirolimus (CCI-779) in patients with extensive-stage small-cell lung cancer who have responding or stable disease after induction chemotherapy: a trial of the Eastern Cooperative Oncology Group (E1500)*. J Thorac Oncol 2007 Nov;2(11):1036-41 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17975496>.

Back to top

## 2.55.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.56 Optimal dose and fractionation of prophylactic cranial irradiation

---

### Contents

- 1 What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with extensive stage SCLC?
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

### 2.56.1 What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with extensive stage SCLC?

---

The Prophylactic Cranial Irradiation Overview Collaborative Group meta-analysis of individual patient data from seven trials included mostly patients with limited stage SCLC although a minority had extensive stage SCLC.<sup>[1]</sup> This analysis confirmed a reduction in the incidence of brain metastases with increasing doses of prophylactic cranial irradiation (PCI), but no effect on survival.

A randomised EORTC trial of PCI in patients with extensive stage SCLC utilised a range of PCI doses and fractionation schemes, the commonest of which were 20Gy/5Fr, 30Gy/10Fr, 30Gy/12Fr and 25gy/10Fr.<sup>[2]</sup> Sixty two percent of patients received 20Gy/5Fr. However, allocation to radiotherapy dose/fractionation schedule was not randomised.

As such, the optimal radiotherapy dose and fractionation schedule for extensive stage SCLC has not yet been defined.

[Back to top](#)

## 2.56.2 Evidence summary and recommendations

Evidence summary	Level	References
Prophylactic cranial radiotherapy schedules ranging from 20Gy in 5 fractions to 30Gy in 12 fractions reduce the incidence of brain metastases and improve survival in extensive stage SCLC patients who achieve a response to initial therapy.	II	[2]
Over this dose range, higher radiotherapy doses confer no survival advantage over lower ones	I	[1]

Evidence-based recommendation	Grade
For patients with extensive stage small cell lung cancer who achieve a response to initial therapy, a range of prophylactic cranial irradiation dose schedules from 20Gy in 5 fractions to 30Gy in 10 fractions is reasonable.	<b>B</b>

Practice point
There is insufficient evidence to recommend a particular prophylactic cranial irradiation dose or fractionation schedule over any other. However, since extensive stage small cell lung cancer has a median survival of less than a year, a short fractionation schedule (20Gy in 5 fractions) is recommended for most patients.

[Back to top](#)

### 2.56.3 References

---

1. ↑ <sup>1.0</sup> <sup>1.1</sup> Prophylactic Cranial Irradiation Overview Collaborative Group. *Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission (review)*. Cochrane Database Syst Rev 2009 Jan Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002805/pdf>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. *Prophylactic cranial irradiation in extensive small-cell lung cancer*. N Engl J Med 2007 Aug 16;357(7):664-72 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17699816>.

[Back to top](#)

### 2.56.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.57 Thoracic radiotherapy

---

### Contents

- 1 Is there a role for thoracic radiotherapy in patients with extensive stage SCLC?
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.57.1 Is there a role for thoracic radiotherapy in patients with extensive stage SCLC?

Two trials employing modern radiotherapy techniques and platinum containing chemotherapy have investigated thoracic radiotherapy as part of the initial management of extensive stage small cell lung cancer patients.<sup>[1][2]</sup>

Jeremic et al. performed a single institution randomised trial of concurrent chemo-radiotherapy versus chemotherapy alone in 206 patients who had achieved a CR in their extra-thoracic disease after three chemotherapy cycles and at least a PR in their chest.<sup>[1]</sup> The addition of thoracic radiotherapy resulted in a statistically significant survival advantage. Apart from radiotherapy-related oesophagitis in about a quarter of patients, no further significant radiotherapy toxicities were observed.

Yee et al.<sup>[2]</sup> performed a prospective single arm trial of consolidative thoracic radiotherapy in patients achieving an objective response to chemotherapy. In this small trial, maximal toxicity was grade 2 oesophagitis in 56% of patients. Similar to the trial of Jeremic et al. no further radiotherapy related toxicities were observed.

The role of thoracic radiotherapy in extensive stage small cell lung cancer is currently being addressed through two cooperative group trials (RTOG 0937 and CREST).

[Back to top](#)

## 2.57.2 Evidence summary and recommendations

Evidence summary	Level	References
Thoracic radiotherapy improved overall survival at the cost of moderate toxicity in a single institution randomised trial.	II	[1]

Evidence-based recommendation	Grade
There is insufficient evidence at present to definitively recommend thoracic radiotherapy as part of the initial management of extensive stage small cell lung cancer.	<b>C</b>

Practice point
In extensive stage small cell lung cancer patients of good performance status who achieve a complete chemotherapy response at extra-thoracic disease sites and some response in their chest disease, consolidative chest radiotherapy could be considered.

[Back to top](#)

## 2.57.3 References

---

1. ↑ <sup>1.0</sup> <sup>1.1</sup> <sup>1.2</sup> Jeremic B, Shibamoto Y, Nikolic N, Milicic B, Milisavljevic S, Dagovic A, et al. *Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study.* J Clin Oncol 1999 Jul;17(7):2092-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10561263>.
2. ↑ <sup>2.0</sup> <sup>2.1</sup> Yee D, Butts C, Reiman A, Joy A, Smylie M, Fenton D, et al. *Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small cell lung cancer.* Radiother Oncol 2011 Sep 17 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21930323>.

[Back to top](#)

## 2.57.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.58 Palliative care in symptom management

---

### Contents

- 1 What is the role of palliative care in symptom management for patients with lung cancer?
  - 1.1 Introduction
  - 1.2 Symptom management
    - 1.2.1 Pain
    - 1.2.2 Dyspnoea
    - 1.2.3 Constipation

1.2.4 Cough
1.2.5 Haemoptysis
2 Evidence summary and recommendations
3 References
4 Appendices

## 2.58.1 What is the role of palliative care in symptom management for patients with lung cancer?

### 2.58.1.1 Introduction

Palliative care is appropriate for all people facing life threatening disease, though in practice in Australia, most services are directed toward people with life limiting/terminal disease. While most studies reviewed to create the palliative care section are derived from studies relating to patients with NSCLC, it is likely that the themes and concepts are broadly applicable to those with SCLC.

Palliative care prioritises the early identification, assessment and management of pain and other symptoms and attention to the psychosocial and spiritual priorities. Substantial evidence demonstrates that palliative care—when combined with standard cancer care or as the main focus of care—leads to better patient and caregiver outcomes; improvement in symptoms, QOL, patient satisfaction, and reduced caregiver burden. Earlier involvement of palliative care also leads to more appropriate referral to and use of hospice, and reduced use of futile intensive care.<sup>[1]</sup> Expert consensus from the American Society of Clinical Oncology thus recommends that combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden.<sup>[2]</sup>

[Back to top](#)

### 2.58.1.2 Symptom management

The occurrence of multiple symptoms is common in cancer with high levels of distress occurring in patients with lung cancer.<sup>[3]</sup> These guidelines will address updates on the more common symptoms of pain, dyspnoea, constipation, cough and haemoptysis. It will not address the use of chemotherapy or radiation therapy for symptom management (refer to *Radiotherapy to the lung primary in stage IV NSCLC*). The majority of studies quoted involve a heterogeneous population and include data from non-cancer patients.

[Back to top](#)

#### 2.58.1.2.1 Pain

Poorly controlled pain requires prompt attention. There is currently good evidence to support the use of nonsteroidals, opioids, bisphosphonates, radiotherapy and radiopharmaceuticals for the management of cancer pain.<sup>[4]</sup>

Morphine remains the recommended opioid based on familiarity, cost and ease of access. A systematic review of 54 randomised studies<sup>[5]</sup> demonstrated that both oral modified release (Mm/r) and immediate release (MIR) morphine is effective for cancer pain. Dose titration occurred with both MIR and Mm/r with studies comparing Mm/r with MIR, MIR of different strengths, MIR with other opioids and different routes of administration. Daily doses ranged from 25mg to 2000mg with an average of between 100mg and 250mg. There was insufficient comparable data for meta-analysis or number need to treat (NNT) for the analgesic effect.

The Cochrane reviews of 43 studies for hydromorphone for acute and chronic pain<sup>[6]</sup> and nine randomised studies methadone for cancer pain. A meta-analysis of four RCT's<sup>[7]</sup> comparing oral oxycodone with oral morphine or oral hydromorphone showed that there was no evidence that mean pain scores differed between oxycodone and control drugs. The efficacy and tolerability of oxycodone was similar to morphine, supporting its use as an opioid for cancer-related pain.

A Cochrane review of the use of non-steroidal anti-inflammatory drugs (NSAIDs), alone or in combination with opioids for cancer pain.<sup>[8]</sup> showed a superiority of NSAID's over placebo no superiority or efficacy of one NSAID over another.

Newer anticonvulsants such as gabapentin and pregabalin are recommended for the management of neuropathic pain.<sup>[9]</sup> The main body of evidence arises for its use in post herpetic neuralgia and diabetic neuropathy though there remains to be head to head trials of these agents.

Data from a systematic review of 30 randomised studies showed benefit for the use of bisphosphonates for the relief of pain from bone metastasis.<sup>[10]</sup> Pooled data from the treatment group achieved a NNT at four weeks of eleven [95% CI 6-36], at twelve weeks of seven [95% CI 5-12] and a number need to harm (NNH) of 16 [95% CI 12-27] for discontinuation of therapy. Small study numbers and limited data precluded exploration of the most effective bisphosphonate and their relative effectiveness. In cases of pain from widespread bony metastasis, intravenous radiopharmaceuticals should be considered. A systematic review<sup>[11]</sup> which included 5-10% of patients with lung cancer concluded that single agent radiopharmaceuticals such as strontium-89 and samarium-153 were effective in the palliation of multiple site of bone pain when conventional treatment was unsatisfactory.

There remains a lack of high quality RCT's to generate substantive evidence for the use of complementary therapies.<sup>[12][13][14]</sup> A systematic review of three RCT's<sup>[12]</sup> showed the effect of auricular acupuncture compared with auricular acupuncture at 'placebo' points with significant decrease in pain intensity recorded on VAS at one month and two months ( $p < 0.0001$ ) and an over all 36% decrease in pain intensity. A systematic review of the benefits of aromatherapy and massage showed benefit but little evidence for the improvement of pain.<sup>[14]</sup>

[Back to top](#)

### **2.58.1.2.2 Dyspnoea**

Dyspnoea is a subjective symptom with complex multifocal phenomenon. It occurs in up to 73% of patient with end stage lung cancer and is associated with a poor prognosis.



The use of oral or parenteral opioids to palliative dyspnoea are well established. Seven trials assessing opioids in a systematic review evaluating interventions for cancer related dyspnoea.<sup>[15]</sup> showed that the administration of subcutaneous morphine resulted in a significant reduction in dyspnoea compared to placebo. There was no benefit from nebulised morphine when compared to subcutaneous morphine.

Oxygen is frequently prescribed but a meta-analysis of 134 cancer patients<sup>[16]</sup> and a detailed systematic review of RCT's involving adults with chronic end stage disease (including cancer) showed that oxygen failed to improve dyspnoea in mildly or non-hypoxemic cancer patients . A more recent international, multicentre, double blind RCT of 239 participants with life limiting illness once again showed no additional symptomatic benefit of oxygen compared to room air.<sup>[17]</sup>

Benzodiazepines are also commonly used in the management of breathlessness but a systematic review of seven studies showed no evidence for a beneficial effect.<sup>[18]</sup> There was a slight, non significant trend towards a beneficial effect, justifying its use as a second or third line treatment. The addition of benzodiazepines to morphine have been shown to be more beneficial than the use of morphine alone.<sup>[15]</sup>

Data from a systematic review of non-pharmacological interventions for breathlessness from 47 studies.<sup>[19]</sup> included complex interventions and were conducted in non-cancer patients and occasionally within a laboratory setting. There was a lack of strong evidence to support the interventions and it remains unclear as to which combinations of interventions are most appropriate.

A study of 30 lung cancer patients referred to a breathless clinic with physiotherapy led interventions showed improvements<sup>[20]</sup> in the frequency of dyspnoea, functional capacity ( $p < 0.001$ ) and degree of breathlessness with the percentage of patients experiencing breathlessness several times or more a day reduced from 73% to 27% four weeks later.

[Back to top](#)

### **2.58.1.2.3 Constipation**

Data from a systematic review<sup>[21]</sup> evaluating the use of laxatives in 616 palliative care patients from seven studies concluded that insufficient RCT's still limit recommendations as to which of the oral laxatives are most appropriate. No differences were demonstrated between lactulose and senna, lactulose and senna compared to magnesium hydrochloride and liquid paraffin or between misrakasneham and senna. Lactulose and senna were more favourable than co-danthramer in stool frequency but not in patient's assessment of bowel function.

More promising results emerged from combined analysis (287 participants) of methylnaltrexone compared to placebo. It significantly induced laxation at four hours (odds ratio 6.95; 95% CI 3.83-12.61). Patients were more likely to experience flatulence and dizziness, but showed no evidence of opioid withdrawal. There is insufficient data about the long term effects of the use of opioid antagonists.

[Back to top](#)

### 2.58.1.2.4 Cough

A phase II study of hydrocodone<sup>[22]</sup> in patients with advanced cancer showed that it was effective in reducing the severity, frequency of cough and associated symptoms. A further detailed systematic review of interventions for cough in cancer<sup>[23]</sup> examined the results of 17 RCT's. No practice recommendations were concluded due to the absence of credible evidence. No clear conclusions were possible from the use of pharmacological interventions though butamirate linctus, codeine (60mg), dihydrocodeine (10mg), cromoglycate and hydropropizine / levodropropizine seem to exercise positive benefits. Brachtherapy was shown to improve cough in selected patients and is possibly beneficial at the lowest effective dose to minimise side effects.

[Back to top](#)

### 2.58.1.2.5 Haemoptysis

A recent study reviewing the benefit of tranxemic acid in a randomised double-blinded placebo controlled trial failed to show its benefit in shortening the number of days of haemoptysis.<sup>[24]</sup> A low incidence of side effects confirmed the relative safety of this drug.

Low level evidence suggests the potential usefulness of transcatheter arterial embolisation (TAE)<sup>[25]</sup> or bronchial artery embolisation.<sup>[26]</sup> Data for 128 TAE procedures completed in 58 patients showed high technical (100%) and clinical success (98%) with a 40% reoccurrence rate. BAE showed an 84% technical success rate though the survival rate in patients with cancer related haemoptysis remained poor. (Refer also to *Radiotherapy to the Lung Primary in Stage IV*)

[Back to top](#)

## 2.58.2 Evidence summary and recommendations

Evidence summary	Level	References
Oral morphine remains the gold standard for the management of moderate to severe cancer pain. It is possible to titrate to analgesic effect using immediate or modified release morphine.	I	[5]
Oxycodone, hydromorphone and methadone can provide comparable analgesia to morphine when titrated to effect.	I	[27] , [28] , [29]
NSAIDS alone is superior to placebo and adequate for the management of mild cancer pain	I	[30]
Bisphosphonates and radiopharmaceuticals should be considered where analgesics and /or radiotherapy are inadequate for the management of painful bone metastasis.	I	[31] , [32]

Evidence-based recommendation	Grade
There is strong evidence from consistent randomised trials to support the use of NSAIDs and opioids for the management of pain in patients with NSCLC.	<b>B</b>

Evidence-based recommendation	Grade
There is a role for the use of bisphosphonates and radiopharmaceuticals in a select group of patients with pain arising from multiple site of bony metastasis.	<b>B</b>

Practice point
<ul style="list-style-type: none"> <li>- It is advised that the use of methadone occurs with involvement of specialist palliative care or pain services, due to its complex pharmacodynamic properties.</li> <li>- The choice of opioids used may consider issues of availability, cost and individual patient factors such as route of administration, metabolism and organ impairment such as renal failure.</li> <li>- Anticonvulsants such as gabapentin and pregabalin may be considered in the management of neuropathic pain, based on substantive body of evidence generated in non-cancer patients.</li> <li>- Non-pharmacological approaches and complementary therapies may be considered as part of a multimodal approach when pain remains poorly controlled.</li> </ul>

Evidence summary	Level	References
The evidence suggest that systemic opioids, administered orally or parenterally is beneficial for the management of dyspnoea in lung cancer patients.	I	[15]
The evidence suggests that both air and oxygen and administered intranasally provide equal symptomatic benefit for the relief of dyspnoea. The benefit of oxygen is better established in patients with hypoxemia.	I	[16], [33], [15]

Evidence-based recommendation	Grade
The use of opioids are recommended for the relief of dyspnoea in patients with NSCLC.	<b>B</b>

Evidence-based recommendation	Grade
Following individual patient assessment and a therapeutic trial, oxygen administered intranasally may be administered to patients with advanced lung cancer to palliate the symptom of breathlessness.	<b>B</b>

Practice point
The use of non-pharmacological strategies, such as breathing retraining, simple relaxation, activity pacing and psychosocial support from nursing or allied health, can be beneficial for the management of breathlessness.

Practice point
Benzodiazepines can be used as a second or third line therapy in the treatment of breathlessness in patients with advanced lung cancer, when opioids and non-pharmacological measures have failed.

Evidence summary	Level	References
The evidence suggests that opioid receptor antagonists such as methylnaltrexone, are effective in inducing laxation for opioid induced constipation.	I	[21]

Evidence-based recommendation	Grade
Subcutaneous methylnaltrexone should be considered in patients where conventional laxatives have failed.	<b>B</b>

#### Practice point

Recommendations for the treatment of constipation in the palliative care population have been made based on expert opinion and currently suggest a combination of stimulant and softening agent.

#### Practice point

- Centrally acting oral opioids may be considered for the suppression of cough in NSCLC
- Symptomatic treatment with antimuscuranic agents or antibiotics may be helpful by reducing the volume of secretions or mucopurulent sputum.
- Where appropriate and accessible, interventions such as brachytherapy may be beneficial for the management of cough in selected patients. (Refer to *Brachytherapy section in Radiotherapy Stage IV*)

#### Practice point

Palliative measures for the management of haemoptysis include the use of oral haemostatics e.g. tranexamic acid, or radiotherapy, or laser treatment to the tumour site and the active management of underlying causes, such as infection, or pulmonary infarction.

[Back to top](#)

### 2.58.3 References

1. ↑ Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. *Early palliative care for patients with metastatic non-small-cell lung cancer*. N Engl J Med 2010 Aug 19;363(8):733-42 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20818875>.
2. ↑ Smith TJ, Temin S, Alesi ER, Abernethy AP, Balboni TA, Basch EM, et al. *American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care*. J Clin Oncol 2012 Mar 10;30(8):880-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22312101>.
3. ↑ Cooley ME. *Symptoms in adults with lung cancer. A systematic research review*. J Pain Symptom Manage 2000 Feb;19(2):137-53 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10699541>.
4. ↑ Lorenz KA, Lynn J, Dy SM, Shugarman LR, Wilkinson A, Mularski RA, et al. *Evidence for improving palliative care at the end of life: a systematic review*. Ann Intern Med 2008 Jan 15;148(2):147-59 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18195339>.

5. ↑ <sup>5.0</sup> <sup>5.1</sup> Wiffen PJ, McQuay HJ. *Oral morphine for cancer pain*. Cochrane Database Syst Rev 2007 Oct 17; (4):CD003868 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17943804>.
6. ↑ Quigley C. *Hydromorphone for acute and chronic pain*. Cochrane Database Syst Rev 2009 Available from: [http://onlinelibrary.wiley.com/doi/cochrane/clsystrev/articles/CD003447/pdf\\_fs.html](http://onlinelibrary.wiley.com/doi/cochrane/clsystrev/articles/CD003447/pdf_fs.html).
7. ↑ Reid CM, Martin RM, Sterne JA, Davies AN, Hanks GW. *Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials*. Arch Intern Med 2006 Apr 24;166(8):837-43 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16636208>.
8. ↑ McNicol E, Strassels SA, Goudas L, Lau J, Carr DB. *NSAIDs or paracetamol, alone or combined with opioids, for cancer pain*. Cochrane Database Syst Rev 2005 Jan 25;(1):CD005180 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15654708>.
9. ↑ Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. *Pharmacologic management of neuropathic pain: evidence-based recommendations*. Pain 2007 Dec 5;132(3):237-51 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17920770>.
10. ↑ Wong R, Wiffen PJ. *Bisphosphonates for the relief of pain secondary to bone metastases*. Cochrane Database Syst Rev 2002;(2):CD002068 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12076438>.
11. ↑ Bauman G, Charette M, Reid R, Sathya J. *Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review*. Radiother Oncol 2005 Jun;75(3):258-70 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16299924>.
12. ↑ <sup>12.0</sup> <sup>12.1</sup> Paley CA, Johnson MI, Tashani OA, Bagnall AM. *Acupuncture for cancer pain in adults*. Cochrane Database Syst Rev 2011 Jan 19;(1):CD007753 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21249694>.
13. ↑ Robb KA, Bennett MI, Johnson MI, Simpson KJ, Oxberry SG. *Transcutaneous electric nerve stimulation (TENS) for cancer pain in adults*. Cochrane Database Syst Rev 2008 Jul 16;(3):CD006276 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18646140>.
14. ↑ <sup>14.0</sup> <sup>14.1</sup> Fellowes D, Barnes K, Wilkinson S. *Aromatherapy and massage for symptom relief in patients with cancer*. Cochrane Database Syst Rev 2004;(2):CD002287 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15106172>.
15. ↑ <sup>15.0</sup> <sup>15.1</sup> <sup>15.2</sup> <sup>15.3</sup> Ben-Aharon I, Gafter-Gvili A, Paul M, Leibovici L, Stemmer SM. *Interventions for alleviating cancer-related dyspnea: a systematic review*. J Clin Oncol 2008 May 10;26(14):2396-404 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18467732>.
16. ↑ <sup>16.0</sup> <sup>16.1</sup> Uronis HE, Currow DC, McCrory DC, Samsa GP, Abernethy AP. *Oxygen for relief of dyspnoea in mildly- or non-hypoxaemic patients with cancer: a systematic review and meta-analysis*. Br J Cancer 2008 Jan 29;98(2):294-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18182991>.
17. ↑ Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE 2nd, Marcello J, et al. *Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial*. Lancet 2010 Sep 4;376(9743):784-93 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20816546>.
18. ↑ Simon ST, Higginson IJ, Booth S, Harding R, Bausewein C. *Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults*. Cochrane Database Syst Rev 2010 Jan 20;(1):CD007354 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20091630>.
19. ↑ Bausewein C, Booth S, Gysels M, Higginson I. *Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases*. Cochrane Database Syst Rev 2008 Apr 16;(2):CD005623 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18425927>.

20. ↑ Hatelý J, Laurence V, Scott A, Baker R, Thomas P. *Breathlessness clinics within specialist palliative care settings can improve the quality of life and functional capacity of patients with lung cancer*. *Palliat Med* 2003 Jul;17(5):410-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12882259>.
21. ↑ <sup>21.0</sup> <sup>21.1</sup> Candy B, Jones L, Goodman ML, Drake R, Tookman A. *Laxatives or methylnaltrexone for the management of constipation in palliative care patients*. *Cochrane Database Syst Rev* 2011 Jan 19;(1): CD003448 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21249653>.
22. ↑ Homsí J, Walsh D, Nelson KA, Sarhill N, Rybicki L, Legrand SB, et al. *A phase II study of hydrocodone for cough in advanced cancer*. *Am J Hosp Palliat Care* 2002;19(1):49-56 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12171425>.
23. ↑ Molassiotis A, Bailey C, Caress A, Brunton L, Smith J. *Interventions for cough in cancer*. *Cochrane Database Syst Rev* 2010 Sep 8;(9):CD007881 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20824870>.
24. ↑ Tscheikuna J, Chvaychoo B, Naruman C, Maranetra N. *Tranexamic acid in patients with hemoptysis*. *J Med Assoc Thai* 2002 Apr;85(4):399-404 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12118485>.
25. ↑ Dave, B.R., Sharma, A., Kalva, S.P., Wicky, S.. *Nine-year single-center experience with transcatheter arterial embolization for haemoptysis: medium-term outcomes*. *Vasc. Endovascular. Surg.* 2011;45, 258-268 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21444351>.
26. ↑ Wang GR, Ensor JE, Gupta S, Hicks ME, Tam AL. *Bronchial artery embolization for the management of hemoptysis in oncology patients: utility and prognostic factors*. *J Vasc Interv Radiol* 2009 Jun;20(6):722-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19406667>.
27. ↑ Quigley C. *Hydromorphone for acute and chronic pain*. *Cochrane Database Syst Rev* 2009 Available from: [http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD003447/pdf\\_fs.html](http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD003447/pdf_fs.html).
28. ↑ Reid CM, Martin RM, Sterne JA, Davies AN, Hanks GW. *Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials*. *Arch Intern Med* 2006 Apr 24;166(8):837-43 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16636208>.
29. ↑ Nicholson AB. *Methadone for cancer pain*. *Cochrane Database Syst Rev* 2007 Oct 17;(4):CD003971 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17943808>.
30. ↑ McNicol E, Strassels SA, Goudas L, Lau J, Carr DB. *NSAIDs or paracetamol, alone or combined with opioids, for cancer pain*. *Cochrane Database Syst Rev* 2005 Jan 25;(1):CD005180 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15654708>.
31. ↑ Wong R, Wiffen PJ. *Bisphosphonates for the relief of pain secondary to bone metastases*. *Cochrane Database Syst Rev* 2002;(2):CD002068 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12076438>.
32. ↑ Bauman G, Charette M, Reid R, Sathya J. *Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review*. *Radiother Oncol* 2005 Jun;75(3):258-70 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16299924>.
33. ↑ Cranston JM, Crockett A, Currow D. *Oxygen therapy for dyspnoea in adults*. *Cochrane Database Syst Rev* 2008 Jul 16;(3):CD004769 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18646110>.

Back to top

## 2.58.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.59 Advance care planning and referral

---

### **Contents**

- 1 What is the role of advance care planning and timing of referral for patients with lung cancer?
  - 1.1 Introduction
  - 1.2 Timing of referral
  - 1.3 Advance care planning
  - 1.4 Efficacy and acceptability of advance care planning
  - 1.5 Need for advance care planning
  - 1.6 Process of advance care planning
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices



## 2.59.1 What is the role of advance care planning and timing of referral for patients with lung cancer?

---

### 2.59.1.1 Introduction

Palliative care is appropriate for all people facing life threatening disease, though in practice in Australia, most services are directed toward people with life limiting/terminal disease. While most studies reviewed to create the palliative care section are derived from studies relating to patients with NSCLC, it is likely that the themes and concepts are broadly applicable to those with SCLC.

Metastatic lung cancer is a leading cause of death. In 2009, it was the leading cause of cancer deaths in Australian men and women and was responsible for the deaths of 7,786 Australians, making it the fourth leading cause of death.<sup>[1]</sup> The prognosis after the diagnosis of stage IV (metastatic) lung cancer has been estimated to be less than one year.<sup>[2]</sup> Due to the high mortality rate, the rapidity of disease progression which is sometimes seen, as well as late presentation and co-morbidities, questions regarding timing of referral to palliative care along with questions regarding advance care planning are highly relevant to this patient group.

[Back to top](#)

### 2.59.1.2 Timing of referral

There has been debate over the optimal time of referral to palliative care for patients diagnosed with advanced cancer, including patients with stage IV lung cancer. Temel et al<sup>[2]</sup> conducted a randomised controlled trial (RCT) to answer this question comparing early referral to palliative care (within eight weeks of diagnosis of metastatic NSCLC) to usual care (including referral to palliative care when requested by patient, family or treating oncologist). Patients who were referred early to palliative care had better quality of life (QOL) assessed 12 weeks after referral, and the improvement in their QOL was both statistically and clinically significant. In addition, patients referred to palliative care early were more likely to have their wishes with respect to resuscitation documented, had less depression and were less likely to receive aggressive care at the end of life. Furthermore, those who were referred early lived an average of 2.7 months longer than those who received usual care. A survival benefit for patients with lung cancer referred to palliative care earlier was also found in a study which extracted data from a large US database and found longer survival for patients referred to hospice than those not referred.<sup>[3]</sup>

[Back to top](#)

### **2.59.1.3 Advance care planning**

Advance care planning (ACP) is a patient centred process in which patients, in consultation with family members and health care providers, make decisions regarding their future health care known should they later become incapable of expressing such preferences.<sup>[4]</sup> The process of advance care planning usually occurs over a series of conversations, rather than being a single 'one off' event. Reviewing patients priorities and preferences as their illness progresses is almost always appropriate.<sup>[5]</sup> Given the poor prognosis of stage IV inoperable lung cancer such discussions would appear to be highly relevant. This type of discussion requires effective communications skills, and guidance regarding these skills may be found in some excellent Australian clinical practice guidelines.<sup>[6]</sup>

[Back to top](#)

### **2.59.1.4 Efficacy and acceptability of advance care planning**

One randomised controlled trial has assessed the efficacy and acceptability of ACP in Australian populations.<sup>[4]</sup> This study randomised elderly, hospitalised inpatients with non malignant disease to an ACP intervention facilitated by a specially trained health care professional. It found patients who completed ACP were more likely to have their preferences known and respected at end of life. Importantly, patients who were randomised to the ACP arm of this trial reported higher levels of satisfaction with care for the inpatient episode in which the ACP occurred. In addition, lower levels of distress and depression were reported by family members of patients who died after completing ACP than those who did not participate in ACP. Qualitative research where patients were interviewed regarding their experience of undertaking ACP discussions confirms that the process of ACP is acceptable to patients.<sup>[7]</sup>

[Back to top](#)

### **2.59.1.5 Need for advance care planning**

Good health care can only be achieved when clinicians and patients share a common understanding of the patients' illness, prognosis and preferences. Information regarding prognosis is highly valued by patients and their families,<sup>[8]</sup> however, with respect to lung cancer, clinicians may not adequately communicate prognosis.<sup>[9]</sup> Patients with other solid malignancies tend to overestimate their prognosis, however this issue has not been addressed in patients with lung cancer.<sup>[10]</sup> In addition, patients often overestimate the probability of success of aggressive interventions like CPR and may not understand the role of such interventions in the context of their advanced cancer.<sup>[11][12][13]</sup>

A minority of patients with advanced lung cancer have had discussions regarding resuscitation status with their clinicians.<sup>[14][15]</sup> A substantial proportion of those who have not discussed their preferences would like to do so, but cite lack of initiation of these discussions by health care practitioners as a major barrier.<sup>[16][12]</sup> When patients have not completed an advance care plan their next of kin may not fully understand their wishes.<sup>[12]</sup> In

contrast, when advance care directives have been completed, bereaved family members report it was helpful in guiding care prior to death.<sup>[17]</sup> In addition, there is a mismatch between doctors' perceptions of patients' preferences with respect to CPR, as well as other life sustaining interventions, and their patients' actual preferences.<sup>[18][19]</sup> Finally, there is evidence to suggest that referral to palliative care at the time of diagnosis increases the likelihood of documenting patients' wishes with respect to resuscitation and avoiding aggressive care at end of life.<sup>[2]</sup>

[Back to top](#)

### **2.59.1.6 Process of advance care planning**

Initiating and facilitating discussions with patients and their families is a complex communication task for which some excellent Australian clinical practice guidelines exist.<sup>[6]</sup> It is important to emphasise that ACP is a process rather than a single conversation, and the involvement of loved ones is almost always appropriate.<sup>[5]</sup>

A systematic review examining patient preferences with respect to end of life discussions found that patients and their care givers want honest information delivered with sensitivity and hope, but without jargon by a trusted health professional.<sup>[8]</sup> They value compassion, care and empathy in the delivery of this type of information.<sup>[8]</sup> However, the information needs of patients and their care givers may vary over time, with patients preferring less information as death approaches and care givers desiring more, reinforcing the need to regularly ask patients and loved ones if they would like to re-explore these issues.<sup>[8]</sup> In addition, there are cultural factors which may impact on information needs and some patients with lung cancer experience stigma which complicate communication and information needs.<sup>[20]</sup>

There is marked variation between individuals in terms of their information needs and decision making preferences. These need to be respected for successful ACP. A Belgian study reported that patients with advanced lung cancer had diverse opinions regarding what they wanted to know, who should be involved in discussions and whom they thought should be involved in making decisions at end of life.<sup>[21]</sup> Some patients prefer to almost unilaterally make their own decisions while others prefer medical staff to have ultimate decision making authority.<sup>[21]</sup> In addition, a patients religious or spiritual beliefs may influence their desire to participate in ACP, with one study suggesting that those who were more reliant on spiritual coping were less likely to engage in ACP discussions.<sup>[22]</sup> Taken together, this evidence suggests the importance of exploring patient understanding and preferences as well as the importance communication skills which use obtaining permission before delving further into these areas.

In terms of the tools to assist ACP, an Australian randomised controlled trial found that the provision of a prompt list to patients increased both the number of questions asked and the number of topics covered in prognostic and end of life discussions,<sup>[23]</sup> suggesting a role for similar tools in ACP. As mentioned above, patients tend to

overestimate the likelihood of success of life sustaining interventions like CPR.<sup>[13]</sup> Relatively simple educational tools which describe the success rate of CPR via the use of a written scenario have been shown to be effective in reducing patient preference for this type of intervention.<sup>[11]</sup> When decisions to limit life prolonging interventions are made, it is important to then emphasise the care that will be provided to the patient in their routine care as well as during the process of dying.<sup>[24]</sup> As with all medical care, it is important to document the outcomes of these types of discussions.

[Back to top](#)

## 2.59.2 Evidence summary and recommendations

Evidence summary	Level	References
The evidence suggests that referral to palliative care at the time of diagnosis of metastatic lung cancer is associated with better outcomes in terms of quality of life, survival and aggressiveness of care at the end of life.	II	[2]

Evidence-based recommendation	Grade
It is recommended to refer patients with stage IV inoperable NSCLC to palliative care at the time of diagnosis of metastatic disease.	<b>B</b>

Evidence summary	Level	References
The evidence suggests that advance care planning is effective and acceptable to Australian populations. The benefits of completing ACP include higher rates of preferences known and respected at end of life, higher patient and family satisfaction and lower rates of family distress and depression.	II	[4]

Evidence-based recommendation	Grade
Advance care planning discussions should be initiated with patients, as there are multiple benefits.	<b>B</b>

Evidence summary	Level	References
The evidence suggests that there is a need for patient centred advance care	II, IV	[2], [14], [15],

Evidence summary	Level	References
planning to address the gaps between clinician and patient expectation and to better understand patients' preferences.		[16], [12], [17], [18], [19]

Evidence-based recommendation	Grade
Clinicians may explore patients' understanding of their health situation and offer to provide further information about their prognosis and to explore the patients' goals/priorities/fears and concerns about the future.	<b>C</b>

Evidence summary	Level	References
The evidence suggests that in the area of prognostic and end of life communication, the provision of a prompt list increases the number of questions asked and the number of topics discussed.	II	[23]

Evidence-based recommendation	Grade
It is recommended to offer the opportunity to discuss advance care plans with patients and their care givers using communication strategies tailored to individual needs, with the assistance of simple tools, like a prompt list, where appropriate.	<b>B</b>

Practice point
If appropriate or necessary to discuss specific treatment options (e.g. CPR), first check the person's understanding of the likely outcomes then provide clarification as needed.

### Practice point

If the decision is made to limit life prolonging treatment (e.g. CPR/ ICU level care etc), emphasise other care and support that will be given to patients, such as other appropriate medical care, symptom directed care and care during the dying process.

[Back to top](#)

## 2.59.3 References

1. ↑ Australian Bureau of Statistics. *3303.0 - Causes of Death, Australia, 2009*. 2009; Accessed 18/06/2011 Available from: <http://www.abs.gov.au/ausstats/abs@.nsf/Products/B6940E9BF2695EE1CA25788400127B0A?opendocument>.
2. ↑ <sup>2.0 2.1 2.2 2.3 2.4</sup> Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. *Early palliative care for patients with metastatic non-small-cell lung cancer*. N Engl J Med 2010 Aug 19;363(8): 733-42 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20818875>.
3. ↑ Connor SR, Pyenson B, Fitch K, Spence C, Iwasaki K. *Comparing hospice and nonhospice patient survival among patients who die within a three-year window*. J Pain Symptom Manage 2007 Mar;33(3): 238-46 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17349493>.
4. ↑ <sup>4.0 4.1 4.2</sup> Detering KM, Hancock AD, Reade MC, Silvester W. *The impact of advance care planning on end of life care in elderly patients: randomised controlled trial*. BMJ 2010 Mar 23;340:c1345 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20332506>.
5. ↑ <sup>5.0 5.1</sup> Emanuel LL, Danis M, Pearlman RA, Singer PA. *Advance care planning as a process: structuring the discussions in practice*. J Am Geriatr Soc 1995 Apr;43(4):440-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7706637>.
6. ↑ <sup>6.0 6.1</sup> Clayton JM, Hancock KM, Butow PN, Tattersall MH, Currow DC, Adler J, et al. *Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers*. Med J Aust 2007 Jun 18;186(12 Suppl):S77, S79, S83-108 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17727340>.
7. ↑ Horne G, Seymour J, Shepherd K. *Advance care planning for patients with inoperable lung cancer*. Int J Palliat Nurs 2006 Apr;12(4):172-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16723962>.
8. ↑ <sup>8.0 8.1 8.2 8.3</sup> Parker SM, Clayton JM, Hancock K, Walder S, Butow PN, Carrick S, et al. *A systematic review of prognostic/end-of-life communication with adults in the advanced stages of a life-limiting illness: patient/caregiver preferences for the content, style, and timing of information*. J Pain Symptom Manage 2007 Jul;34(1):81-93 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17531434>.
9. ↑ Griffin JP, Nelson JE, Koch KA, Niell HB, Ackerman TF, Thompson M, et al. *End-of-life care in patients with lung cancer*. Chest 2003 Jan;123(1 Suppl):312S-331S Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12527587>.
10. ↑ Weeks JC, Cook EF, O'Day SJ, Peterson LM, Wenger N, Reding D, et al. *Relationship between cancer patients' predictions of prognosis and their treatment preferences*. JAMA 1998 Jun 3;279(21):1709-14 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9624023>.

11. ↑ <sup>11.0</sup> <sup>11.1</sup> Sears SR, Woodward JT, Twillman RK. *What do I have to lose? Effects of a psycho-educational intervention on cancer patient preference for resuscitation.* J Behav Med 2007 Dec;30(6):533-44 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17712617>.
12. ↑ <sup>12.0</sup> <sup>12.1</sup> <sup>12.2</sup> <sup>12.3</sup> Phipps E, True G, Harris D, Chong U, Tester W, Chavin SI, et al. *Approaching the end of life: attitudes, preferences, and behaviors of African-American and white patients and their family caregivers.* J Clin Oncol 2003 Feb 1;21(3):549-54 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12560448>.
13. ↑ <sup>13.0</sup> <sup>13.1</sup> Mead GE, Turnbull CJ. *Cardiopulmonary resuscitation in the elderly: patients' and relatives' views.* J Med Ethics 1995 Feb;21(1):39-44 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7776347>.
14. ↑ <sup>14.0</sup> <sup>14.1</sup> Fairchild A, Kelly KL, Balogh A. *In pursuit of an artful death: discussion of resuscitation status on an inpatient radiation oncology service.* Support Care Cancer 2005 Oct;13(10):842-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15846524>.
15. ↑ <sup>15.0</sup> <sup>15.1</sup> Reichner CA, Thompson JA, O'Brien S, Kuru T, Anderson ED. *Outcome and code status of lung cancer patients admitted to the medical ICU.* Chest 2006 Sep;130(3):719-23 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16963668>.
16. ↑ <sup>16.0</sup> <sup>16.1</sup> Huskamp HA, Keating NL, Malin JL, Zaslavsky AM, Weeks JC, Earle CC, et al. *Discussions with physicians about hospice among patients with metastatic lung cancer.* Arch Intern Med 2009 May 25;169(10):954-62 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19468089>.
17. ↑ <sup>17.0</sup> <sup>17.1</sup> Bakitas M, Ahles TA, Skalla K, Brokaw FC, Byock I, Hanscom B, et al. *Proxy perspectives regarding end-of-life care for persons with cancer.* Cancer 2008 Apr 15;112(8):1854-61 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18306393>.
18. ↑ <sup>18.0</sup> <sup>18.1</sup> Teno JM, Hakim RB, Knaus WA, Wenger NS, Phillips RS, Wu AW, et al. *Preferences for cardiopulmonary resuscitation: physician-patient agreement and hospital resource use. The SUPPORT Investigators.* J Gen Intern Med 1995 Apr;10(4):179-86 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7790978>.
19. ↑ <sup>19.0</sup> <sup>19.1</sup> Claessens MT, Lynn J, Zhong Z, Desbiens NA, Phillips RS, Wu AW, et al. *Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments.* J Am Geriatr Soc 2000 May;48(5 Suppl):S146-53 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10809468>.
20. ↑ Chapple A, Ziebland S, McPherson A. *Stigma, shame, and blame experienced by patients with lung cancer: qualitative study.* BMJ 2004 Jun 19;328(7454):1470 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15194599>.
21. ↑ <sup>21.0</sup> <sup>21.1</sup> Pardon K, Deschepper R, Stichele RV, Bernheim J, Mortier F, Deliens L, et al. *Preferences of advanced lung cancer patients for patient-centred information and decision-making: a prospective multicentre study in 13 hospitals in Belgium.* Patient Educ Couns 2009 Dec;77(3):421-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19828279>.
22. ↑ True G, Phipps EJ, Braitman LE, Harralson T, Harris D, Tester W. *Treatment preferences and advance care planning at end of life: the role of ethnicity and spiritual coping in cancer patients.* Ann Behav Med 2005 Oct;30(2):174-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16173914>.



23. ↑ <sup>23.0</sup> <sup>23.1</sup> Clayton JM, Butow PN, Tattersall MH, Devine RJ, Simpson JM, Aggarwal G, et al. *Randomized controlled trial of a prompt list to help advanced cancer patients and their caregivers to ask questions about prognosis and end-of-life care.* J Clin Oncol 2007 Feb 20;25(6):715-23 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17308275>.
24. ↑ Clayton JM, Butow PN, Arnold RM, Tattersall MH. *Fostering coping and nurturing hope when discussing the future with terminally ill cancer patients and their caregivers.* Cancer 2005 May 1;103(9):1965-75 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15789360>.

[Back to top](#)

## 2.59.4 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.60 Psychological support and interventions

---

### Contents

- 1 What is the role of psychological support and interventions in the treatment of lung cancer?
  - 1.1 Introduction
  - 1.2 Psychosocial treatment of depression
  - 1.3 Psychosocial treatment of anxiety
  - 1.4 Psychosocial treatment of fatigue
  - 1.5 Psychosocial treatment of pain
  - 1.6 Quality of life
  - 1.7 Conclusion



2 Evidence summary and recommendations

- 2.1 Depression
- 2.2 Anxiety
- 2.3 Fatigue
- 2.4 Pain
- 2.5 Quality of life

3 References

4 Appendices

## 2.60.1 What is the role of psychological support and interventions in the treatment of lung cancer?

### 2.60.1.1 Introduction

Palliative care is appropriate for all people facing life threatening disease, though in practice in Australia, most services are directed toward people with life limiting/terminal disease. While most studies reviewed to create the palliative care section are derived from studies relating to patients with NSCLC, it is likely that the themes and concepts are broadly applicable to those with SCLC.

Lung cancer patients' have been found to have a significantly higher burden of unmet psychological need compared to other cancer patients,<sup>[1]</sup> with studies quoting up to 43% of lung cancer patients experiencing psychological distress compared with approximately 35% of patients with other cancer diagnoses.<sup>[2]</sup> The psychological distress of lung cancer patients has been found to persist throughout the clinical course of illness<sup>[3]</sup> as poor prognosis, symptom severity and treatment side-effects of lung cancer adversely affects psychological wellbeing.<sup>[4]</sup> Early identification, treatment, screening and timely referrals are important first steps in the management of psychological distress and optimising quality of life (QoL) in these patients.<sup>[5][6]</sup>

These guidelines will provide direction for non-pharmacological evidence-based management of common psychological problems seen in the NSCLC population, including depression, anxiety, fatigue, pain and disruption to QoL. These guidelines have been developed following review of current literature, taking into account the limited number of randomised control trials, small sample sizes, heterogenous samples and high attrition rates in this population.

[Back to top](#)

### 2.60.1.2 Psychosocial treatment of depression

There have been four recent systematic reviews<sup>[7][8][9][10]</sup> and one meta-analysis<sup>[11]</sup> evaluating the efficacy of psychological interventions for the treatment of depression in samples of mixed cancer patients.

Barsevic et al<sup>[7]</sup> in a systematic review of 36 studies, including two well conducted meta-analyses (N= 22,319), concluded that psycho-educational interventions benefited cancer patients with depressive symptomatology. In regard to content of these studies the authors concluded that 70% of behaviour therapy studies, 66% of counseling studies and 58% of studies that tested behaviour and counseling in combination with cancer education were effective. Uitterhoeve et al<sup>[10]</sup> conducted a systematic review of psychosocial interventions specifically for patients with advanced cancer. The review included 10 RCTs (N=862) involving 13 trials, and reported that behaviour therapy improved mood in advanced cancer patients in 12 out of 13 trials.

A systematic review by Newell et al<sup>[8]</sup> and a meta-analysis by Osborne et al<sup>[11]</sup> suggested that that Cognitive Behaviour Therapy (CBT) was effective in the management of depression particularly in the short-term.

The literature provides moderate support for the use of psychotherapy interventions in group settings for reducing the impact of depression in cancer patients. Newell et al, in a systematic review of 15 trials of psychological interventions, concluded that a variety of psychotherapeutic interventions including group therapy, education, structured counseling, and CBT, warrant further investigation to justify their use, but that tentative recommendations could be made for the use of group psychotherapy, education and structured counseling for depressed patients with cancer.<sup>[8]</sup> A further systematic review by Williams et al concluded that CBT, counselling and psychotherapy and group social support were all effective in reducing symptoms of depression in patients with cancer, including lung cancer.<sup>[9]</sup> Also, Uitterhoeve et al found that patient self-esteem and mood improved with a combination of behavioural therapy and group support. In contrast, Osborne et al found that individual interventions were more effective than group interventions for treatment of depression, anxiety and quality of life in cancer survivors.<sup>[11]</sup> This inconsistency in the literature may reflect different sample characteristics, for example Osborne et al's meta-analysis focused on cancer survivors, whereas the two reviews<sup>[8],[9]</sup> involved either a mixed sample of cancer survivors or focused on patients with advanced cancer. All three reviews commented on inconsistencies in the methodological quality of studies examined, whilst Newell et al provided a summary of quality indicators to ensure methodological rigour of future studies could be improved.<sup>[8]</sup>

[Back to top](#)

### 2.60.1.3 Psychosocial treatment of anxiety

CBT remains the recommended first line treatment for anxiety in non-cancer populations, few studies have evaluated its efficacy in patients with lung cancer

The evidence supporting the use of CBT as a treatment for anxiety in advanced cancer remains inconclusive. Moorey et al. conducted a small randomized control trial (RCT) of 80 participants with advanced cancer comparing a control group (usual care) with CBT. Results suggested that participants receiving CBT had consistently lower anxiety over time.<sup>[12]</sup> Newell et al in a systematic review did not find consistent evidence for the use of CBT to treat anxiety,<sup>[8]</sup> however Osborne et al's meta-analysis found that CBT for anxiety had a large effect in a sample of cancer survivors ( $g=1.99$   $p<0.01$ ; 95% CI 0.69- 3.31).<sup>[11]</sup>

The benefits of group interventions for cancer patients with anxiety remain unclear. A systematic review involving 13 trials found only one trial, involving a Supportive Group Psychotherapy intervention, had a positive impact on anxiety. This trial involved women with metastatic breast cancer only, therefore the results cannot be generalize to NSCLC population.<sup>[10]</sup> In a recent pilot RCT, 90 patients with stage III or stage IV advanced cancer were randomly assigned to Meaning Centered Group Psychotherapy (MCGP) or Supportive Group Psychotherapy (SGP) with results suggesting that participants in the MCGP group, in addition to showing greater improvements in spiritual well-being and sense of meaning also showed improvement in anxiety, whereas participants in the SGP did not show any improvements in these areas.<sup>[13]</sup>

[Back to top](#)

### 2.60.1.4 Psychosocial treatment of fatigue

The numbers of psychological interventions that specifically target fatigue are limited as fatigue is typically measured as a secondary outcome to depression or QoL. The available literature suggests that psychological interventions may assist in the treatment of fatigue.<sup>[14][15][16]</sup>

A Cochrane systematic review of “psychosocial interventions for reducing fatigue during cancer treatment in adults” identified 27 studies involving 3324 participants that specifically targeted fatigue as an outcome. Only five of these studies utilised psychological interventions to specifically treat fatigue.<sup>[17]</sup> Of these latter studies, four studies indicated that they were effective in treating fatigue and two of these studies indicated that the effects were maintained at follow-up whilst small sample size may have reduced the effectiveness of one study. The Cochrane review found that the fatigue specific programs had three main components:

- 1) fatigue education;
- 2) self-care and coping techniques; and
- 3) activity management learning to balance activity and rest.

These interventions were also short interventions consisting of three sessions and varying durations from 10 to 60 minutes per session. Researchers also found three interventions that were not targeting fatigue as their primary outcome to have a significant effect on fatigue. The content of these three interventions included both supportive and unstructured therapy approaches or CBT.<sup>[17]</sup> Overall the Cochrane review concluded that evidence for fatigue management was weak to moderate with fatigue specific interventions having better outcomes.

Kangas et al<sup>[18]</sup> conducted a systematic review and meta-analysis of 57 RCTs of non-pharmacological studies that had fatigue or tiredness as an outcome, and concluded that both exercise and psychological interventions reduced cancer-related fatigue with no significant differences between these two interventions whilst psychological interventions that used supportive expressive and CBT modalities were also found to have a moderate effect in reducing fatigue.<sup>[18]</sup> Similarly to the Cochrane review,<sup>[17]</sup> Kangas et al concluded that these studies, which specifically targeted fatigue in their hypothesis, yielded larger effect sizes.

[Back to top](#)

### 2.60.1.5 Psychosocial treatment of pain

RCTs evaluating the efficacy of psychological support in reducing pain specifically in NSCLC cancer patients are not available.

Devine et al performed a meta-analysis of 25 psychological intervention studies, published from 1978 -2001, which included data from 1723 adults with cancer. The authors found that relaxation-based interventions, relaxation and cognitive behavioural interventions, educational and supportive counseling interventions resulted in generally beneficial effects on pain outcomes, and when the analysis was limited to the three studies employing group randomization the effect on pain was statistically significant ( $d+ = 0.33$ ,  $95\%CI=0.07-0.59$ ).<sup>[19]</sup> Relaxation and cognitive-based interventions were effective in reducing pain shortly after treatment and were acceptable to patients, however the authors concluded that the long-term effects of these interventions are unknown in this population.

The results of one RCT, utilising psycho-education strategies versus standard care, found that psycho-educational strategies resulted in statistically and clinically significant reductions in pain.<sup>[20]</sup> In a more recent and innovative intervention study,<sup>[20]</sup> patients with advanced colorectal, lung, prostate and gynecological cancer, received education and training to use an MP3 player loaded with 12 cognitive behavioural strategies (e. g.: relaxation, guided imagery). These patients demonstrated a significant reduction in pain both immediately before and after the use of CBT strategies.<sup>[21]</sup>

[Back to top](#)

### 2.60.1.6 Quality of life

Uttierhoeve et al<sup>[10]</sup> conducted a systemic review of literature published between 1990 and 2002 regarding psychological interventions for people with advanced cancer. They concluded that behavioural therapy had positive effects on QoL domains, including improvements in mood, coping and functional living . Graves<sup>[22]</sup> in a meta-analysis found that interventions that were based in social cognitive therapy including self -efficacy and self-regulation lead to global improvement in QoL. Furthermore meta-analysis involving the impact of CBT on QoL in cancer survivors found that CBT had large positive long-term effect on QoL ( $g = 0.91$ ,  $p<0.01$ ;  $95\% CI-0.38-1.44$ ).<sup>[11]</sup>

A Cochrane review of non-invasive intervention aimed at improving QoL of lung cancer patients found that two nursing interventions aimed at managing breathlessness and three structured programs improved patients mood symptoms and performance status.<sup>[23]</sup>

[Back to top](#)

### 2.60.1.7 Conclusion

The diagnosis of stage IV NSCLC impacts on physical, psychological well-being and QoL of patients. The Psychosocial Guidelines for Adults with Cancer<sup>[6]</sup> identifies disease factors such as stage of disease, and poor prognosis as risk factors for increased distress. These factors, together with other patient characteristics including psychiatric history, drug and alcohol use, age, social support, co-morbid medical conditions and socio-economic status, are predictors of psychological distress and will affect individual capacity to adjust to incurable disease. Research demonstrates that psychological interventions can assist in improving psychological well-being and coping with physical symptoms of disease and treatment. Combinations of CBT, psycho-education, relaxation, supportive and unstructured therapies appear to be the most beneficial in this group of patients.

[Back to top](#)

## 2.60.2 Evidence summary and recommendations

### 2.60.2.1 Depression

Evidence summary	Level	References
Psycho-educational interventions assist in treating depressive symptomatology in patient with cancer (in group or individual format).	I	[7], [10]
Cognitive Behaviour Therapy (CBT) is effective in the management of depression, particularly in the short-term (in group or individual format).	I	[8], [9], [10], [11]

Evidence-based recommendation	Grade
Psycho-educational interventions including: counseling, behaviour therapy, education /information giving, and social support will assist in ameliorating the impact of depression.	<b>B</b>

Evidence-based recommendation	Grade
There is reasonable evidence from systematic reviews to support the use of Cognitive Behaviour Therapy (CBT) in the management of depression particularly in the short-term (in group or individual format). Further randomised controlled trials involving adequately powered studies and consistent methodology should be conducted.	<b>B</b>

### 2.60.2.2 Anxiety

Evidence summary	Level	References
Cognitive Behaviour Therapy (CBT) may have an effective role as a treatment of anxiety in NSCLC cancer population.	I, II	[11], [12], [24], [25]
Supportive and Meaning-based Group Psychotherapies have a positive impact on anxiety.	I, II	[10], [13]

Evidence-based recommendation	Grade
Cognitive Behaviour Therapy (CBT) is recommended for the treatment of anxiety in NSCLC. Further randomised controlled trials involving adequately powered studies and consistent methodology should be conducted.	<b>B</b>

Evidence-based recommendation	Grade
Supportive and Meaning based group psychotherapies, may be helpful in reducing anxiety in NSCLC patients. Further randomised controlled trials involving adequately powered studies and consistent methodology should be conducted.	<b>B</b>

### 2.60.2.3 Fatigue

Evidence summary	Level	References
Psychotherapeutic intervention including Cognitive Behaviour Therapy (CBT), education, self-care strategies, behavioural interventions, activity management, supportive psychotherapy have all been found to ameliorate fatigue. Psychological interventions that specifically target fatigue are the most beneficial.	I, II	[14], [15], [17], [18], [16]

Evidence-based recommendation	Grade
Psychological interventions including Cognitive Behaviour Therapy (CBT), education, self-care strategies, behavioural interventions, activity management, supportive psychotherapy have all been found to ameliorate fatigue.	<b>C</b>

Evidence-based recommendation	Grade
Further randomised controlled trials involving adequately powered studies and consistent methodology can be conducted to ascertain unmet needs in advanced cancer.	

#### 2.60.2.4 Pain

Evidence summary	Level	References
Evidence suggests that Cognitive Behaviour Therapy (CBT), relaxation-based interventions (eg: guided imagery, progressive muscle relaxation) supportive psychotherapies and psycho-educational strategies have role in pain management.	I, II	[19], [20], [21]

Evidence-based recommendation	Grade
Psychological interventions have an important role in the management of cancer related pain.	<b>B</b>

#### 2.60.2.5 Quality of life

Evidence summary	Level	References
Evidence suggests that behavioural, cognitive and social cognitive therapies may be useful in improving coping, adjustment, functional ability and quality of life.	I	[10], [11], [22], [23]
Non- invasive nurse-led programs aimed to target symptom management lead to improvement in wellbeing and quality of life.	I	[23]

Evidence-based recommendation	Grade
Quality of life of lung patients may improve with behavioural, cognitive or social cognitive therapies.	<b>C</b>

Evidence-based recommendation	Grade
Non-invasive nurse-led programs with a focus on managing physical symptoms and treatment related toxicities may be used to optimise quality of life.	<b>C</b>

Back to top

### 2.60.3 References

1. ↑ Li J, Girgis A. *Supportive care needs: are patients with lung cancer a neglected population?* *Psychooncology* 2006 Jun;15(6):509-16 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16292789>.
2. ↑ Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. *The prevalence of psychological distress by cancer site.* *Psychooncology* 2001;10(1):19-28 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11180574>.
3. ↑ Akechi T, Okuyama T, Akizuki N, Azuma H, Sagawa R, Furukawa TA, et al. *Course of psychological distress and its predictors in advanced non-small cell lung cancer patients.* *Psychooncology* 2006 Jun;15(6):463-73 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16173112>.
4. ↑ Kurtz ME, Kurtz JC, Stommel M, Given CW, Given B. *Predictors of depressive symptomatology of geriatric patients with lung cancer-a longitudinal analysis.* *Psychooncology* 2002;11(1):12-22 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11835589>.
5. ↑ Néron S, Correa JA, Dajczman E, Kasymjanova G, Kreisman H, Small D. *Screening for depressive symptoms in patients with unresectable lung cancer.* *Support Care Cancer* 2007 Oct;15(10):1207-12 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17879108>.
6. ↑ <sup>6.0</sup> <sup>6.1</sup> National Breast Cancer Centre and National Cancer Control Initiative. *Clinical practice guidelines for the psychosocial care of adults with cancer.* National Breast Cancer Centre, Camperdown, NSW 2003 Available from: [http://www.nhmrc.gov.au/\\_files\\_nhmrc/publications/attachments/cp90.pdf](http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp90.pdf).
7. ↑ <sup>7.0</sup> <sup>7.1</sup> <sup>7.2</sup> Barsevick AM, Sweeney C, Haney E, Chung E. *A systematic qualitative analysis of psychoeducational interventions for depression in patients with cancer.* *Oncol Nurs Forum* 2002;29(1):73-84; quiz 85-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11817494>.
8. ↑ <sup>8.0</sup> <sup>8.1</sup> <sup>8.2</sup> <sup>8.3</sup> <sup>8.4</sup> <sup>8.5</sup> <sup>8.6</sup> Newell SA, Sanson-Fisher RW, Savolainen NJ. *Systematic review of psychological therapies for cancer patients: overview and recommendations for future research.* *J Natl Cancer Inst* 2002 Apr 17;94(8):558-84 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11959890>.
9. ↑ <sup>9.0</sup> <sup>9.1</sup> <sup>9.2</sup> <sup>9.3</sup> Williams S, Dale J. *The effectiveness of treatment for depression/depressive symptoms in adults with cancer: a systematic review.* *Br J Cancer* 2006 Feb 13;94(3):372-90 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16465173>.
10. ↑ <sup>10.0</sup> <sup>10.1</sup> <sup>10.2</sup> <sup>10.3</sup> <sup>10.4</sup> <sup>10.5</sup> <sup>10.6</sup> <sup>10.7</sup> Uitterhoeve RJ, Vernooy M, Litjens M, Potting K, Bensing J, De Mulder P, et al. *Psychosocial interventions for patients with advanced cancer - a systematic review of the literature.* *Br J Cancer* 2004 Sep 13;91(6):1050-62 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15316564>.



11. ↑ <sup>11.0 11.1 11.2 11.3 11.4 11.5 11.6 11.7</sup> Osborn RL, Demoncada AC, Feuerstein M. *Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses*. Int J Psychiatry Med 2006;36(1):13-34 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16927576>.
12. ↑ <sup>12.0 12.1</sup> Moorey S, Cort E, Kapari M, Monroe B, Hansford P, Mannix K, et al. *A cluster randomized controlled trial of cognitive behaviour therapy for common mental disorders in patients with advanced cancer*. Psychol Med 2009 May;39(5):713-23 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18761755>.
13. ↑ <sup>13.0 13.1</sup> Breitbart W, Rosenfeld B, Gibson C, Pessin H, Poppito S, Nelson C, et al. *Meaning-centered group psychotherapy for patients with advanced cancer: a pilot randomized controlled trial*. Psychooncology 2010 Jan;19(1):21-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19274623>.
14. ↑ <sup>14.0 14.1</sup> Ream E, Richardson A, Alexander-Dann C. *Supportive intervention for fatigue in patients undergoing chemotherapy: a randomized controlled trial*. J Pain Symptom Manage 2006 Feb;31(2):148-61 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16488348>.
15. ↑ <sup>15.0 15.1</sup> Armes J, Chalder T, Addington-Hall J, Richardson A, Hotopf M. *A randomized controlled trial to evaluate the effectiveness of a brief, behaviorally oriented intervention for cancer-related fatigue*. Cancer 2007 Sep 15;110(6):1385-95 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17661342>.
16. ↑ <sup>16.0 16.1</sup> Jacobsen PB, Donovan KA, Vadaparampil ST, Small BJ. *Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue*. Health Psychol 2007 Nov;26(6):660-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18020836>.
17. ↑ <sup>17.0 17.1 17.2 17.3</sup> Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. *Psychosocial interventions for reducing fatigue during cancer treatment in adults*. Cochrane Database Syst Rev 2009 Jan 21;(1):CD006953 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19160308>.
18. ↑ <sup>18.0 18.1 18.2</sup> Kangas M, Bovbjerg DH, Montgomery GH. *Cancer-related fatigue: a systematic and meta-analytic review of non-pharmacological therapies for cancer patients*. Psychol Bull 2008 Sep;134(5):700-41 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18729569>.
19. ↑ <sup>19.0 19.1</sup> Devine EC. *Meta-analysis of the effect of psychoeducational interventions on pain in adults with cancer*. Oncol Nurs Forum 2003;30(1):75-89 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12515986>.
20. ↑ <sup>20.0 20.1 20.2</sup> Miaskowski C, Dodd M, West C, Paul SM, Schumacher K, Tripathy D, et al. *The use of a responder analysis to identify differences in patient outcomes following a self-care intervention to improve cancer pain management*. Pain 2007 May;129(1-2):55-63 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17257753>.
21. ↑ <sup>21.0 21.1</sup> Kwekkeboom KL, Abbott-Anderson K, Wanta B. *Feasibility of a patient-controlled cognitive-behavioral intervention for pain, fatigue, and sleep disturbance in cancer*. Oncol Nurs Forum 2010 May;37(3):E151-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20439200>.
22. ↑ <sup>22.0 22.1</sup> Graves KD. *Social cognitive theory and cancer patients' quality of life: a meta-analysis of psychosocial intervention components*. Health Psychol 2003 Mar;22(2):210-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12683741>.
23. ↑ <sup>23.0 23.1 23.2</sup> Solà I, Thompson E, Subirana M, López C, Pascual A. *Non-invasive interventions for improving well-being and quality of life in patients with lung cancer*. Cochrane Database Syst Rev 2004 Oct 18;(4):CD004282 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15495096>.

24. ↑ Greer JA, Park ER, Prigerson HG, Safren SA. *Tailoring Cognitive-Behavioral Therapy to Treat Anxiety Comorbid with Advanced Cancer*. J Cogn Psychother 2010 Jan 1;24(4):294-313 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21234281>.
25. ↑ Rolke HB, Bakke PS, Gallefoss F. *Health related quality of life, mood disorders and coping abilities in an unselected sample of patients with primary lung cancer*. Respir Med 2008 Oct;102(10):1460-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18590954>.

[Back to top](#)

## 2.60.4 Appendices

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.61 Optimal management of malignant pleural effusions

### Contents

- 1 What is the role of early ICC/pleurodesis or early thoroscopic pleurodesis in the treatment of pleural effusions in patients with stage IV inoperable NSCLC?
  - 1.1 Introduction
  - 1.2 Prevention of fluid re-accumulation
  - 1.3 Sclerosant pleurodesis
  - 1.4 Pleurodesis using video-assisted thoracoscopy (VATS)
  - 1.5 Pleurodesis using an intercostal catheter insertion and injection of sclerosant
  - 1.6 Choice of sclerosant
  - 1.7 What catheter size should be used?
  - 1.8 Tunnelled pleural catheters
- 2 Evidence summary and recommendations
- 3 References

## 2.61.1 What is the role of early ICC/pleurodesis or early thoracoscopic pleurodesis in the treatment of pleural effusions in patients with stage IV inoperable NSCLC?

### 2.61.1.1 Introduction

The accumulation of pleural fluid is an important cause of breathlessness in patients with lung cancer and mesothelioma as it can be with secondary malignancy involving the lung. The mechanisms that underpin the breathlessness are not well defined but are likely to extend beyond the effect of lung compression/deflation. Large pleural effusions can influence the properties of the chest wall and the function of the diaphragm. Imbalance between respiratory effort and diaphragm motion may contribute to the complex sensation that is breathlessness.<sup>[1][2]</sup> Therefore, symptomatic benefit from draining effusions with apparently minimal lung expansion can be seen, if not consistently.

Interventions to drain pleural effusions in patients with an established diagnosis of lung cancer should generally be performed unless

1. The effusion is small
2. Breathlessness can reasonably be attributed to another cause
3. The prognosis is poor and breathlessness can be addressed by other means<sup>[3]</sup>

[Back to top](#)

### 2.61.1.2 Prevention of fluid re-accumulation

Large pleural effusions re-accumulate after simple aspiration with only the rate of such re-accumulation varying. When symptoms were present and significant these will recur. The options for active management of pleural fluid begin with repeated simple aspiration. This approach should be reserved for patients with very poor prospects for survival but in whom aspiration produces a clinical benefit. The evidence that fluid recurs and that interventions are effective is based on clinical experience and before-after comparisons of fluid accumulation in patients in many intervention studies but randomised comparisons of simple aspiration with other interventions are lacking. In patients with better performance status, repeated simple aspiration may establish the sequence of events that lead to adhesion formation that can in the future make pleural adhesions more difficult or less effective. Insertion of an indwelling intercostal catheter alone, without any attempt at pleurodesis, is not recommended.<sup>[3]</sup>

[Back to top](#)

### 2.61.1.3 Sclerosant pleurodesis

Pleurodesis is an intervention designed to create inflammation of the pleura with the aim that adhesions will develop between visceral (inner) and parietal (outer) layers of pleura. This requires drainage of pleural fluid in the first instance and then injection of the sclerosant. An acute inflammatory reaction develops and in the process adhesion develops. The use of (iodised) talc to achieve pleurodesis was first reported for treatment of recurrent pneumothorax<sup>[4]</sup> and chylothorax.<sup>[5]</sup> The subsequent partial or complete obliteration of the pleural cavity alters the pressure dynamics in the pleural space and removes the space that fluid would otherwise recollect in.

The success rate varies with the clinical characteristics of patients and the techniques used. Where the lung does not expand and therefore apposition of the visceral and parietal pleura does not develop, pleurodesis cannot be achieved. Adhesion will not occur at a site of tumour deposit and therefore extensive pleural malignancy reduced the likelihood of success as well. Because of its inflammatory basis, successful pleurodesis can be associated with significant pain and this should be anticipated and addressed in each case.<sup>[6]</sup>

[Back to top](#)

### 2.61.1.4 Pleurodesis using video-assisted thoracoscopy (VATS)

In a patient who is reasonably fit and in whom a diagnosis has not been established based on analysis of pleural fluid, thoracoscopy should be performed as it has the highest diagnostic yield. At the same time, fluid can be fully drained and talc sclerosant can be insufflated to achieve a pleurodesis. Most procedures are performed under general anaesthetic with a rigid thoracoscope using one or two ports of entry. A semi-rigid fiberoptic thoracoscope is also available.<sup>[7]</sup> This has the advantage that the procedure can be readily performed under LA /sedation and areas of the pleural space adjacent to the entry port can be better seen. Biopsies on the other hand are smaller and more superficial and this may be important when mesothelioma is a possibility. VATS should allow the breaking down of adhesions and more complete drainage of pockets of fluid - thereby in some patients achieving pleurodesis with a more fully inflated lung. The advantage that this represents is not quantifiable from published data because those studies comparing VATS with other strategies have not stratified results by the presence of adhesions and adhesions are broken down in the ordinary course of VATS thoracoscopy.

Procedural risks of pleurodesis using VATS are low.<sup>[8][9]</sup> Measurements of 30 day mortality that are relevant in other forms of thoracic surgery are compromised by the nature of the malignancy that demands the procedure. There is a low rate of empyema. Success rate, best measured by failure of fluid re-accumulation requiring a further procedure should be over 80%.<sup>[9][10]</sup> In non-randomised studies and case series, VATS with talc insufflation is superior to intercostal catheter drainage but these studies are significantly biased in favour of VATS that was generally performed on fitter patients.<sup>[11]</sup> RCTs and a Cochrane analysis comparing VATS to ICC drainage using talc slurry as sclerosant show a smaller but still significant advantage in favour of VATS.<sup>[10]</sup> The RR for absence of fluid accumulation was 1.19(1.04-1.36) favouring the thoracoscopic approach.<sup>[12]</sup> The clinical bias for performing this procedure on more fit patients is supported by Australian evidence of poor outcomes in patients undergoing VATS who have ASA scores >3.<sup>[13]</sup>

There are no randomised studies comparing standard 'surgical' VATS with so-called medical thoracoscopy using rigid or semi-rigid instruments and performed under local anaesthetic/sedation. Case series of the latter show a high success rate for pleurodesis by talc insufflation and acceptable safety outcomes<sup>[14]</sup> and the role of medical thoracoscopy in diagnosis and treatment of pleural effusions has been incorporated into guidelines.<sup>[15]</sup>

[Back to top](#)

### 2.61.1.5 Pleurodesis using an intercostal catheter insertion and injection of sclerosant

In this procedure, a catheter is inserted under LA into the pleural space and fluid is drained. After drainage, a mixture of sclerosant and local anesthetic is injected into the pleural space. Pleural fluid drainage continues for 24-48 hours and then the catheter is removed. Longer periods of drainage may not increase the chance of success<sup>[16]</sup> and the practice of leaving the catheter in situ until daily drainage had fallen below a certain volume is not recommended in guidelines (BTS) although the quality of evidence in relation to this question is not strong. Success rate, again measured by failure of fluid re-accumulation requiring any further procedure is over 70%<sup>[9][10][11][12]</sup> Procedural risks should be low if the procedure is performed following current guidelines that include the use of bedside ultrasound.<sup>[17]</sup>

[Back to top](#)

### 2.61.1.6 Choice of sclerosant

Over time, a large number of sclerosants have been used to achieve pleurodesis. Those commonly used in Australia have included formulations of bleomycin and tetracycline (that are no longer available) and talc. Success rates with bleomycin and tetracycline were 50-60%.<sup>[18]</sup> Graded talc is used in almost all pleurodesis procedures in Australia whether by VATS or talc slurry. Only talc that is graded so that fine particles are excluded should be used as ungraded talc is associated with acute respiratory events that can be severe.<sup>[19]</sup> In other parts of the world, small volume solutions of povidone-iodine have been used and achieve success rates similar to talc<sup>[20][21][22]</sup> Povidone-iodine is easily accessible, cheap and appears easier than a talc slurry to prepare for use. It is effective when administered via thoracoscopy or intercostals catheter.<sup>[23]</sup> Only small volumes of iodine should be used as in published papers as iodine toxicity can occur with larger instillations (up to 500mls) as sometimes used in procedures for pleural infection.<sup>[24]</sup>

#### Practice point

Editorial comments on the question of povidone-iodine mention the greater clinical experience with talc and caution against rapid switching to povidone-iodine. This is a reasonable position.

Pain after pleurodesis is associated with pleuritis and procedural effectiveness. Severe pain has been reported with povidone-iodine

[Back to top](#)

### 2.61.1.7 What catheter size should be used?

Historically, large bore (>20F) catheters were used for pleurodesis. The rationale for their continued use after smaller, tube over guide-wire, catheter systems became available was that smaller tubes might become blocked by slurry or viscous pleural drainage. This is now clearly disproven. Intercostal catheters larger than 20F, as traditionally used, do not increase the success rate but do increase complications and pain. Catheters in the range 12-14F are as effective as larger tubes and the evidence for this exists for both talc and povidone-iodine.<sup>[25][26][27]</sup> There is non-randomised evidence for effectiveness with other sclerosants.<sup>[28]</sup>

#### Practice point

Insertion of a small intercostal catheter is not without risk. In particular, standard dilators are long enough to damage major mediastinal structures if inserted an unnecessary distance into the thoracic cavity.

All pleural procedures can be performed by operators with adequate training and experience in accordance with current guidelines and standards. This includes the use of bedside ultrasound.

The two common adverse events that occur with smaller catheters after their successful insertion are dislodgment and blockage. It is wise to secure catheters with sutures and tape and intermittent flushing via a three-way tap to reduce the risk of catheter blockage.

[Back to top](#)

### 2.61.1.8 Tunnelled pleural catheters

Tunnelled pleural catheters (TPCs) are designed to allow ambulatory or home care. The catheter consists of an intrathoracic end, a segment that is tunneled under the skin to the insertion site and a port to which a suction bottle is attached to facilitate intermittent drainage.<sup>[29]</sup> It is generally applied in cases where lung re-expansion has not been achieved, or is not expected, but a benefit of drainage has still been apparent. They can be used after failed pleurodesis.<sup>[30]</sup> Even in cases where re-expansion is not anticipated, there is a small but significant rate of spontaneous pleurodesis.<sup>[31][32]</sup> Compared to other treatment options, it does not require GA, allows earlier ambulation and shortens hospital stay but the drainage bottles are costly and in most circumstances the cost for these is presently met by the patient. Overall, cost effectiveness is greater in patients with shorter life expectancy,<sup>[33]</sup> but the cost transfer from hospital to individual patients is problematic.

### Practice point

Tunnelled pleural catheters (TPC) may be preferred where lung reinflation is not achieved, but consideration of the practicalities of ongoing care may be made before their use.

All pleural procedures can be performed by operators with adequate training and experience in accordance with current guidelines and standards.

[Back to top](#)

## 2.61.2 Evidence summary and recommendations

### Fluid re-accumulation

Evidence summary	Level	References
Significant malignant pleural effusions re-accumulate after simple drainage. Simple aspiration is inferior to drainage with pleurodesis.	I	

Evidence-based recommendation	Grade
For fit patients, with an established diagnosis, an attempt to reduce pleural fluid re-accumulation by pleurodesis may be made at the first opportunity.	<b>A</b>

### Video-assisted thoracoscopy

Evidence summary	Level	References
Thoracoscopy and talc insufflation is the preferred approach to the management of symptomatic malignant pleural effusion in patients with good performance status, as it has the lowest rate of fluid re-accumulation and is safe.	I	[8], [9], [10], [11], [12], [13]

Evidence-based recommendation	Grade
Fitter patients may be offered thoracoscopy. Individual clinical features, access to services and skill mix will determine whether that is a VATS procedure or medical thoracoscopy.	<b>A</b>

### Intercostal catheter pleurodesis

Evidence summary	Level	References
Pleurodesis using a pleural catheter and injection of sclerosant is an effective and safe alternative to VATS procedures albeit with a somewhat lower success rate.	I	[6], [9], [10], [11], [12], [16], [21]

Evidence-based recommendation	Grade
Intercostal catheter (ICC) pleurodesis may be performed in patients unfit for more aggressive interventions and is an acceptable alternative where access to VATS or medical thoracoscopy without delay is problematic.	<b>A</b>

### Choice of sclerosant

Evidence summary	Level	References
Graded talc is a safe and effective sclerosant when used for the purpose of achieving pleurodesis.	I	[8], [9], [10], [11], [12], [16], [21]

Evidence-based recommendation	Grade
Graded talc may be regarded as the current standard, as it is safe, effective and the most commonly used sclerosant.	<b>A</b>

Evidence summary	Level	References
Iodine-povidone solution is an effective sclerosant in the treatment of recurrent pleural effusions in patients with stage IV inoperable lung cancer with similar outcomes to graded talc.	I	[20], [34], [22], [23]

Evidence-based recommendation	Grade
There is a case for wider use of povidone-iodine solutions in Australia.	<b>B</b>

### Catheter size



Evidence summary	Level	References
Talc slurry or povidone-iodone solution should be instilled using a small bore 12-14F catheter. There is no benefit from larger catheters that cause more patient discomfort.	I	[25] , [26] , [27] , [28]

Evidence-based recommendation	Grade
Only smaller-bore, 12-14F, intercostal catheters may be used for attempted bedside pleurodesis in patients with malignant pleural effusions.	<b>A</b>

### Tunnelled pleural catheters

Evidence summary	Level	References
Insertion of a tunnelled pleural catheters is a safe and effective treatment option for patients where the lung does not inflate after aspiration. Tunnelled pleural catheter insertion allows earlier ambulation and shortens hospital stay.	II	[29] , [30] , [31] , [32]

Evidence-based recommendation	Grade
Tunnelled pleural catheters may be considered in patients well enough for a procedure but who have limited life expectancy and where issues of equipment and ongoing clinical care can be addressed.	<b>A</b>

No comment pages found

[Back to top](#)

## 2.61.3 References

1. ↑ Estenne M, Yernault JC, De Troyer A. *Mechanism of relief of dyspnea after thoracocentesis in patients with large pleural effusions*. Am J Med 1983 May;74(5):813-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/6837605>.
2. ↑ Wang JS, Tseng CH. *Changes in pulmonary mechanics and gas exchange after thoracocentesis on patients with inversion of a hemidiaphragm secondary to large pleural effusion*. Chest 1995 Jun;107(6): 1610-4 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7781355>.

3. ↑ <sup>3.0 3.1</sup> Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ, BTS Pleural Disease Guideline Group. *Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010*. Thorax 2010 Aug;65 Suppl 2:ii32-40 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20696691>.
4. ↑ SMITH WG, ROTHWELL PP. *Treatment of spontaneous pneumothorax*. Thorax 1962 Dec;17:342-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/13989598>.
5. ↑ GINGELL JC. *TREATMENT OF CHYLOTHORAX BY PRODUCING PLEURODESIS USING IODIZED TALC*. Thorax 1965 May;20:261-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14292435>.
6. ↑ <sup>6.0 6.1</sup> Sherman S, Ravikrishnan KP, Patel AS, Seidman JC. *Optimum anesthesia with intrapleural lidocaine during chemical pleurodesis with tetracycline*. Chest 1988 Mar;93(3):533-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3342661>.
7. ↑ Ernst A, Hersh CP, Herth F, Thurer R, LoCicero J 3rd, Beamis J, et al. *A novel instrument for the evaluation of the pleural space: an experience in 34 patients*. Chest 2002 Nov;122(5):1530-4 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12426249>.
8. ↑ <sup>8.0 8.1 8.2</sup> Barbetakis N, Asteriou C, Papadopoulou F, Samanidis G, Paliouras D, Kleontas A, et al. *Early and late morbidity and mortality and life expectancy following thoracoscopic talc insufflation for control of malignant pleural effusions: a review of 400 cases*. J Cardiothorac Surg 2010 Apr 19;5:27 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20403196>.
9. ↑ <sup>9.0 9.1 9.2 9.3 9.4 9.5</sup> Cardillo G, Facciolo F, Carbone L, Regal M, Corzani F, Ricci A, et al. *Long-term follow-up of video-assisted talc pleurodesis in malignant recurrent pleural effusions*. Eur J Cardiothorac Surg 2002 Feb;21(2):302-5; discussion 305-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11825740>.
10. ↑ <sup>10.0 10.1 10.2 10.3 10.4 10.5</sup> Dresler CM, Olak J, Herndon JE 2nd, Richards WG, Scalzetti E, Fleishman SB, et al. *Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion*. Chest 2005 Mar;127(3):909-15 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15764775>.
11. ↑ <sup>11.0 11.1 11.2 11.3 11.4</sup> Stefani A, Natali P, Casali C, Morandi U. *Talc poudrage versus talc slurry in the treatment of malignant pleural effusion. A prospective comparative study*. Eur J Cardiothorac Surg 2006 Dec;30(6):827-32 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17113008>.
12. ↑ <sup>12.0 12.1 12.2 12.3 12.4</sup> Shaw P, Agarwal R. *Pleurodesis for malignant pleural effusions*. Cochrane Database Syst Rev 2004;(1):CD002916 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/14973997>.
13. ↑ <sup>13.0 13.1</sup> Trotter D, Aly A, Siu L, Knight S. *Video-assisted thoracoscopic (VATS) pleurodesis for malignant effusion: an Australian teaching hospital's experience*. Heart Lung Circ 2005 Jun;14(2):93-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16352262>.
14. ↑ Lee P, Hsu A, Lo C, Colt HG. *Prospective evaluation of flex-rigid pleuroscopy for indeterminate pleural effusion: accuracy, safety and outcome*. Respirology 2007 Nov;12(6):881-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17986118>.
15. ↑ Rahman NM, Ali NJ, Brown G, Chapman SJ, Davies RJ, Downer NJ, et al. *Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010*. Thorax 2010 Aug;65 Suppl 2:ii54-60 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20696694>.
16. ↑ <sup>16.0 16.1 16.2</sup> Goodman A, Davies CW. *Efficacy of short-term versus long-term chest tube drainage following talc slurry pleurodesis in patients with malignant pleural effusions: a randomised trial*. Lung Cancer 2006 Oct;54(1):51-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16920219>.

17. ↑ Havelock T, Teoh R, Laws D, Gleeson F, BTS Pleural Disease Guideline Group. *Pleural procedures and thoracic ultrasound: British Thoracic Society Pleural Disease Guideline 2010*. Thorax 2010 Aug;65 Suppl 2: ii61-76 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20696688>.
18. ↑ Martínez-Moragón E, Aparicio J, Rogado MC, Sanchis J, Sanchis F, Gil-Suay V. *Pleurodesis in malignant pleural effusions: a randomized study of tetracycline versus bleomycin*. Eur Respir J 1997 Oct;10(10):2380-3 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9387969>.
19. ↑ Campos JR, Werebe EC, Vargas FS, Jatene FB, Light RW. *Respiratory failure due to insufflated talc*. Lancet 1997 Jan 25;349(9047):251-2 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9014915>.
20. ↑ <sup>20.0</sup> <sup>20.1</sup> Olivares-Torres CA, Laniado-Laborín R, Chávez-García C, León-Gastelum C, Reyes-Escamilla A, Light RW. *Iodopovidone pleurodesis for recurrent pleural effusions*. Chest 2002 Aug;122(2):581-3 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12171835>.
21. ↑ <sup>21.0</sup> <sup>21.1</sup> <sup>21.2</sup> Mohsen TA, Zeid AA, Meshref M, Tawfeek N, Redmond K, Ananiadou OG, et al. *Local iodine pleurodesis versus thoracoscopic talc insufflation in recurrent malignant pleural effusion: a prospective randomized control trial*. Eur J Cardiothorac Surg 2011 Aug;40(2):282-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20961772>.
22. ↑ <sup>22.0</sup> <sup>22.1</sup> Agarwal R, Aggarwal AN, Gupta D. *Efficacy and safety of iodopovidone pleurodesis through tube thoracostomy*. Respirology 2006 Jan;11(1):105-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16423210>.
23. ↑ <sup>23.0</sup> <sup>23.1</sup> Agarwal R, Aggarwal AN, Gupta D, Jindal SK. *Efficacy and safety of iodopovidone in chemical pleurodesis: a meta-analysis of observational studies*. Respir Med 2006 Nov;100(11):2043-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16574389>.
24. ↑ Wagenfeld L, Zeitz O, Richard G. *Visual loss after povidone-iodine pleurodesis*. N Engl J Med 2007 Sep 20;357(12):1264-5 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17881764>.
25. ↑ <sup>25.0</sup> <sup>25.1</sup> Parulekar W, Di Primio G, Matzinger F, Dennie C, Bociek G. *Use of small-bore vs large-bore chest tubes for treatment of malignant pleural effusions*. Chest 2001 Jul;120(1):19-25 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11451810>.
26. ↑ <sup>26.0</sup> <sup>26.1</sup> Caglayan B, Torun E, Turan D, Fidan A, Gemici C, Sarac G, et al. *Efficacy of iodopovidone pleurodesis and comparison of small-bore catheter versus large-bore chest tube*. Ann Surg Oncol 2008 Sep;15(9):2594-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18594928>.
27. ↑ <sup>27.0</sup> <sup>27.1</sup> Clementsen P, Evald T, Grode G, Hansen M, Krag Jacobsen G, Faurschou P. *Treatment of malignant pleural effusion: pleurodesis using a small percutaneous catheter. A prospective randomized study*. Respir Med 1998 Mar;92(3):593-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9692129>.
28. ↑ <sup>28.0</sup> <sup>28.1</sup> Sartori S, Tassinari D, Ceccotti P, Tombesi P, Nielsen I, Trevisani L, et al. *Prospective randomized trial of intrapleural bleomycin versus interferon alfa-2b via ultrasound-guided small-bore chest tube in the palliative treatment of malignant pleural effusions*. J Clin Oncol 2004 Apr 1;22(7):1228-33 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15051770>.
29. ↑ <sup>29.0</sup> <sup>29.1</sup> Musani AI, Haas AR, Seijo L, Wilby M, Serman DH. *Outpatient management of malignant pleural effusions with small-bore, tunneled pleural catheters*. Respiration 2004;71(6):559-66 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15627865>.
30. ↑ <sup>30.0</sup> <sup>30.1</sup> Thornton RH, Miller Z, Covey AM, Brody L, Sofocleous CT, Solomon SB, et al. *Tunneled pleural catheters for treatment of recurrent malignant pleural effusion following failed pleurodesis*. J Vasc Interv Radiol 2010 May;21(5):696-700 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20307992>.

31. ↑ <sup>31.0</sup> <sup>31.1</sup> Tremblay A, Michaud G. *Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion*. Chest 2006 Feb;129(2):362-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16478853>.
32. ↑ <sup>32.0</sup> <sup>32.1</sup> Suzuki K, Servais EL, Rizk NP, Solomon SB, Sima CS, Park BJ, et al. *Palliation and Pleurodesis in Malignant Pleural Effusion: The Role for Tunneled Pleural Catheters*. J Thorac Oncol 2011 Feb 15 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21325982>.
33. ↑ Olden AM, Holloway R. *Treatment of malignant pleural effusion: PleuRx catheter or talc pleurodesis? A cost-effectiveness analysis*. J Palliat Med 2010 Jan;13(1):59-65 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19839739>.
34. ↑ Moazami N, Rice TW, Rybicki LA, Adelstein DJ, Murthy SC, DeCamp MM, et al. *Stage III non-small cell lung cancer and metachronous brain metastases*. J Thorac Cardiovasc Surg 2002 Jul;124(1):113-22 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12091816>.

[Back to top](#)

## 2.61.4 Appendices

---

<a href="#">View recommendation components</a>	<a href="#">View pending evidence</a>	<a href="#">View body of evidence</a>	<a href="#">View all comments</a>	<a href="#">View literature search</a>
<a href="#">View PICO</a>				

[Back to top](#)

## 2.62 Case management

---

### Contents

- 1 What is the role of case management in the treatment of patients with lung cancer?
  - 1.1 Introduction
  - 1.2 Lung cancer nurse specialists in initial care
  - 1.3 Lung cancer nurse specialists in the follow-up setting
- 2 Evidence summary and recommendations

3 References

4 Appendices

## 2.62.1 What is the role of case management in the treatment of patients with lung cancer?

### 2.62.1.1 Introduction

Optimal care of patients with advanced lung cancer, perhaps lung cancer at any stage, requires integrated inputs from a range of clinicians. In addition, there are time-critical and generally novel requirements of patients themselves as they both navigate to the clinical assessment, diagnostic test or treatment and do their best to anticipate and then experience a combination of the effects of the disease itself, and of treatment.

At its simplest implementation, case management can be limited to navigation. This is in essence facilitating steps in management – whether that be arranging referral, any associated transport and providing such information to ensure that the steps are carried out. No specific clinical care is provided and such a role could be filled by an individual with sound administrative skills. A step up would be an Oncology Nurse Navigator – a registered nurse with cancer-specific training who guides and supports patients through the challenges of having cancer.<sup>[1]</sup> In its fullest implementation, one sees the Lung Cancer Specialist Nurse (LCNS). A LCNS is part of a multi-disciplinary team and uses experience and clinical skills as well as navigational understanding to contribute to optimising care. The required skill set will depend on the context of care. Some may cover the full spectrum of lung cancer and others concentrated on more specific settings such as Thoracic Surgery or Palliative Care. In most models, the LCNS becomes a primary point of health care contact.

Given the high level of acceptance of the role of Breast Cancer nurses, it should not surprise that a Lung Cancer Nurse would be effective, if in a different fashion. Both diseases represent a challenge to the navigational skills of naïve patients. There are also differences. The effect of disease and treatment on body image is critical for many women facing breast cancer and its treatment options. In many cases there is some time to allow the best choice to be made. In contrast, the lung cancer journey after diagnosis can be characterised by rapidly changing physical and emotional symptoms.

In the United Kingdom, the role of the lung cancer nurse is highly developed. There is an auditable standard that at least 80% of patients are seen by a lung cancer specialist nurse. In a national audit in 2011, the number actually seen was 75% and this has risen by about 5% each year since 2008. Compared to patients who had not been seen by a LCNS, those who were seen were twice as likely to receive active treatment. This might be partly explained by a centre-effect, LCNS being connected to centres and patients too unwell for treatment not reaching these. However, anecdotes and blogs subsequent to the release of these data suggest that this is not the sole explanation<sup>[2]</sup> and the difference persisted after allowance for age and performance status strongly suggesting that this is a real effect.

One of the casual criticisms of the UK implementation of the LCNS model, was that the LCNS would simply be the compassionate face for care poorly delivered and that it was a cheap substitute for modernizing the nature of treatment. The latest audit clearly puts that concern to rest.

One of the challenges in validating the effect of case management or a LCNS is that these are usually just one of a range of interventions delivered simultaneously. Therefore, the specific effectiveness of components or aspects is difficult to determine or prove. This is essentially the finding of an attempted systematic review of case management in cancer<sup>[3]</sup> (although this was not specifically focused on lung cancer). There are flaws in much of the limited literature in this area. There is generally little evidence in relation to lung cancer. Some of the problems include failure to recruit target numbers,<sup>[4]</sup> small proportions of lung cancer subjects,<sup>[5][6]</sup> in addition to the challenge of determining what aspect of a multi-pronged intervention had a specific effect.

[Back to top](#)

### 2.62.1.2 Lung cancer nurse specialists in initial care

The evidence for this rests with the UK national lung cancer audit. It is true that the patients who were not treated may have self-selected themselves and thus had no chance to have nurse contact. However, where recorded this was not reflected in performance status.<sup>[7]</sup> Given that Australian studies have shown low<sup>[8]</sup> and inconsistent<sup>[9]</sup> rates of active treatment it would be wrong to assume that the audit findings in the UK in this regard have no applicability to the local setting.

#### Practice point

The UK standard of 80% involvement of LCNS at the time of lung cancer diagnosis is not a rational one in Australia where lung cancer diagnosis is more de-centralised.

With the above caveat, including a LCNS in the care of patients from early in the diagnosis-decision making stage may be highly valuable.

By extension of the universal acceptance of the role of breast care nurses, it seems more than probable that patients with lung cancer would benefit in a similar fashion.

[Back to top](#)

### 2.62.1.3 Lung cancer nurse specialists in the follow-up setting

Compared to other case management scenarios in lung cancer care this has evaluated in a well designed and executed study.<sup>[10]</sup> Compared to usual lung cancer clinic care, patients whose primary follow-up after initial treatment was conducted by a Lung Cancer Nurse had symptoms identified sooner and received more supplementary radiotherapy. Satisfaction was high and intervention patients scored better with respect to emotional functioning and breathlessness. Satisfaction was high. Implementation of this model of care may be difficult in Australia in the fee-for-service care model rather than the Outpatient Clinic model in the UK. It would also be affected by the skill level of the nurse and may be influenced by the medical comparator - rotating registrar vs consultant.

### Practice point

When a clinical problem develops, the threshold for a patient to contact a nurse is lower than that for contacting a doctor whom they often wish not to trouble.

As lung cancer nurses are introduced to the Australian setting, careful planning will optimise the benefit in improved patient care.

In the rural setting, the lung cancer case load may not be sufficient to justify a lung cancer specific nurse and the optimal plan. may be to increase educational standards of existing nurses with more general roles.

[Back to top](#)

## 2.62.2 Evidence summary and recommendations

### Practice point

Lung cancer nurses can be integral to the care of patients with lung cancer in centres where there is a significant lung cancer case load.

Evidence summary	Level	References
After initial treatment, follow-up by a lung cancer nurse is acceptable to patients, is associated with early recognition of symptoms and results in improved symptom and emotional outcomes.	II	[10]

Evidence-based recommendation	Grade
Lung cancer nurses should be involved in the follow-up care of patients with lung cancer in centres where there is a significant lung cancer case load.  The model of implementation should be flexible.	<b>B</b>

[Back to top](#)



## 2.62.3 References

1. ↑ Swanson J, Koch L. *The role of the oncology nurse navigator in distress management of adult inpatients with cancer: a retrospective study*. *Oncol Nurs Forum* 2010 Jan;37(1):69-76 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20044341>.
2. ↑ Ford, S. *Lung cancer patients twice as likely to get treatment if they see a nurse*. *Nursing Times* 2011 Available from: <http://www.nursingtimes.net/nursing-practice/clinical-specialisms/cancer/lung-cancer-patients-twice-as-likely-to-get-treatment-if-they-see-a-nurse/5038833.article>.
3. ↑ Wulff CN, Thygesen M, Søndergaard J, Vedsted P. *Case management used to optimize cancer care pathways: a systematic review*. *BMC Health Serv Res* 2008 Nov 6;8:227 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18986554>.
4. ↑ Skrutkowski M, Saucier A, Eades M, Swidzinski M, Ritchie J, Marchionni C, et al. *Impact of a pivot nurse in oncology on patients with lung or breast cancer: symptom distress, fatigue, quality of life, and use of healthcare resources*. *Oncol Nurs Forum* 2008 Nov;35(6):948-54 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18980926>.
5. ↑ Seow H, Piet L, Kenworthy CM, Jones S, Fagan PJ, Dy SM. *Evaluating a palliative care case management program for cancer patients: the Omega Life Program*. *J Palliat Med* 2008 Dec;11(10):1314-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19115890>.
6. ↑ Campbell C, Craig J, Eggert J, Bailey-Dorton C. *Implementing and measuring the impact of patient navigation at a comprehensive community cancer center*. *Oncol Nurs Forum* 2010 Jan;37(1):61-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20044340>.
7. ↑ NHS Information Centre. *National Lung Cancer Audit Report*. 2011; Accessed February 2011 Available from: <http://www.hqip.org.uk/assets/NCAPOP-Library/Lung-Cancer-NHS-IC-AUDIT-2011.pdf>.
8. ↑ Vinod SK, O'Connell DL, Simonella L, Delaney GP, Boyer M, Peters M, et al. *Gaps in optimal care for lung cancer*. *J Thorac Oncol* 2008 Aug;3(8):871-9 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18670305>.
9. ↑ Simonella L, O'Connell DL, Vinod SK, Delaney GP, Boyer M, Esmaili N, et al. *No improvement in lung cancer care: the management of lung cancer in 1996 and 2002 in New South Wales*. *Intern Med J* 2009 Jul; 39(7):453-8 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19220546>.
10. ↑ <sup>10.0</sup> <sup>10.1</sup> Moore S, Corner J, Haviland J, Wells M, Salmon E, Normand C, et al. *Nurse led follow up and conventional medical follow up in management of patients with lung cancer: randomised trial*. *BMJ* 2002 Nov 16;325(7373):1145 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12433764>.

Back to top



## 2.62.4 Appendices

---

[View  
recommendation  
components](#)

[View pending  
evidence](#)

[View body of  
evidence](#)

[View all  
comments](#)

[View literature  
search](#)

[View  
PICO](#)

[Back to top](#)

## 2.63 Treatment of rash from anti-EGFR therapy

---

### **Contents**

- 1 What is the role of topical creams, skin moisturisers and maintenance antibiotics in the treatment of rash from anti-EGFR therapy in patients with lung cancer?
  - 1.1 Introduction
  - 1.2 Rash - prophylactic management
  - 1.3 Rash-reactive management
  - 1.4 Dry skin
  - 1.5 Other adverse skin and eye effects
- 2 Evidence summary and recommendations
- 3 References
- 4 Appendices

## 2.63.1 What is the role of topical creams, skin moisturisers and maintenance antibiotics in the treatment of rash from anti-EGFR therapy in patients with lung cancer?

---

### 2.63.1.1 Introduction

A distinctive rash is a common side-effect of treatment with a range of pharmaceutical agents that interact with the epidermal growth factor receptor (EGFR). In relation to lung cancer, the current agents in use are two orally-administered small molecules, erlotinib<sup>[1]</sup> and gefitinib<sup>2</sup>, and a monoclonal antibody cetuximab<sup>[2]</sup> that is given by intravenous infusion. Similar cutaneous adverse effects are seen with other EGFR antagonists used for separate indications.

Although commonly referred to as acne-like, the pathology and clinical appearance is quite dissimilar. Papules and pustules predominate without some specific features of acne such as comedones.<sup>[3]</sup> A variety of alternate or umbrella descriptions have been used but it is best thought of as papulopustular. Onset occurs typically within weeks of treatment onset and some fluctuation of rash severity is commonly seen. The extent of rash can vary from one that is localised and causing few symptoms to a generalized reaction that may be associated with severe itch or tenderness. There is anecdotal evidence that some patients self-adjust the dose or dosing frequency in an attempt to manage the impact of rash. Resolution is seen after cessation of treatment.

Unfortunately, there are limited data derived from randomised clinical trials and a profusion of strategies to address the problem of rash have been proposed and used. A review from a single centre found that 26 different strategies had been initially employed to address rash in 49 patients.<sup>[4]</sup>

Dry skin is a separate, important adverse effect. It tends to occur later in the treatment than does rash. Management of this has generally been along the lines of dermatological treatment of dry skin for other known or unknown causes. Hence little evidence, specific for this clinical setting, has been generated and the prescriber should follow general expert-driven consensus guidance.<sup>[5]</sup>

[Back to top](#)

### 2.63.1.2 Rash - prophylactic management

The aim of prophylactic treatment is to commence this at the same time as the EGFR antagonist, in order to reduce the severity and/or frequency of rash. This is important in patients who may have significant symptoms at the time of treatment commencement and as rash is the side-effect most likely to result in treatment interruption. A number of single or compound interventions have been trialled in this setting. Tetracycline did not reduce the frequency of rash, but it did reduce severity and quality of life scores were better.<sup>[6]</sup> Doxycycline

in combination with moisturisers, in addition to topical steroids and sunscreen, given as prophylaxis was superior to a reactive management plan in patients with colo-rectal cancer given another EGFR-antagonist.<sup>[7]</sup> However, it is known from other studies that steroids and sunscreen have limited or no efficacy so that the treatment effect is likely to be resident in the antibiotic or moisturiser elements of that treatment plan. Minocycline reduced rash severity and there was no additional benefit from adding tazarotene.<sup>[8]</sup> Sunscreen does not prevent rash.<sup>[9]</sup>

#### Practice point

Rash is a common adverse effect and at the commencement of treatment, patients may be informed of this possibility.

Patients can be made aware that the severity of rash may be reduced by prophylactic antibiotic treatment.

Sunscreen cannot be recommended for the purpose of reducing rash. Barrier methods – clothing, hats and limiting time in the sun can be employed in preference.

[Back to top](#)

### 2.63.1.3 Rash-reactive management

The approach to rash as a clinical problem will be influenced to a great extent by the nature of the response of the tumour itself to treatment. The positive association of rash with treatment responses vexes this issue. Where tumour progression has occurred on treatment the EGFR antagonist can be simply ceased. Where treatment must continue, the strongest evidence for treatment effect exists for antibiotics – clindamycin, docycycline and minocycline. This evidence is derived largely from uncontrolled studies and by inference from the few studies in the prophylactic setting. Apparently positive responses in uncontrolled studies could be influenced by natural fluctuations or patient-initiated dose adjustments unknown to investigators. Other agents have been added including isotretinoin,<sup>[10]</sup> but the added value of the second agent is uncertain. There are no meaningful comparative data to support a preference for one or other antibiotic. Uncertainties expressed in consensus guidelines underscore the lack of quality evidence.<sup>[5]</sup>

#### Practice point

For very severe rash, alone or in combination with other skin adverse effects, treatment can be discontinued or suspended.

Evidence for treatments supplementary to antibiotics for rash is presently lacking, but a useful effect cannot be disproven.

**Practice point**

Topical formulations of steroids and tacrolimus do not add to the benefit of antibiotic treatment.

[Back to top](#)

### 2.63.1.4 Dry skin

Drying of the skin occurs on a continuum from a trivial effect to formation of severe fissures for which interventions such as glue can be required. The use of skin moisturising products are presently commonly recommended. There is no meaningful data on which specific recommendations can be based for dry skin in this clinical setting. Empirical treatment has been based on that employed for other xerostoses.

**Practice point**

Anecdotal evidence supports the use of skin moisturisers but data for product selection, frequency of use and consequential outcomes are lacking.

The routine use of moisturisers can be justified at the outset of EGFR-TKI but this is based on expert opinion and reasonable fear of the consequences of inaction not controlled trials.

Severe drying with fissuring can be regarded as a serious complication and the opinion of a Dermatologist, ideally one with an interest in this clinical area, may be sought.

[Back to top](#)

### 2.63.1.5 Other adverse skin and eye effects

Other skin adverse effects including paronychia are seen and are important. Ocular side-effects including but not limited to drying of secretions, conjunctivitis, blepharitis and eyelash misgrowth are also described and can be clinically significant.

[Back to top](#)

## 2.63.2 Evidence summary and recommendations

Evidence summary	Level	References
Prophylactic antibiotic treatment with tetracycline 500mg or doxycycline 100mg/day should be commenced in conjunction with EGFR-TKI inhibitors to reduce the severity or frequency of rash.	II	[6], [7], [8]

Evidence-based recommendation	Grade
Prophylactic antibiotic therapy with tetracycline 500mg or doxycycline 100mg/day should be commenced in conjunction with EGFR-TKI inhibitors as it reduces the severity of rash.	<b>B</b>

Practice point
Patients with clinically significant rash may be commenced on oral antibiotic therapy with tetracycline, minocycline or doxycycline.

Back to top

### 2.63.3 References

1. ↑ Bonomi P. *Erlotinib: a new therapeutic approach for non-small cell lung cancer*. Expert Opin Investig Drugs 2003 Aug;12(8):1395-401 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12882624>.
2. ↑ Baselga J. *The EGFR as a target for anticancer therapy--focus on cetuximab*. Eur J Cancer 2001 Sep;37 Suppl 4:S16-22 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11597400>.
3. ↑ Agero AL, Dusza SW, Benvenuto-Andrade C, Busam KJ, Myskowski P, Halpern AC. *Dermatologic side effects associated with the epidermal growth factor receptor inhibitors*. J Am Acad Dermatol 2006 Oct;55(4):657-70 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17010747>.
4. ↑ Solomon BM, Jatoi A. *Epidermal growth factor receptor (EGFR) inhibitor-induced rash: a consecutive patient series that illustrates the need for rigorous palliative trials*. J Palliat Med 2011 Feb;14(2):153-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21226620>.
5. ↑ <sup>5.0</sup> <sup>5.1</sup> Burtness B, Anadkat M, Basti S, Hughes M, Lacouture ME, McClure JS, et al. *NCCN Task Force Report: Management of dermatologic and other toxicities associated with EGFR inhibition in patients with cancer*. J Natl Compr Canc Netw 2009 May;7 Suppl 1:S5-21; quiz S22-4 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19470276>.
6. ↑ <sup>6.0</sup> <sup>6.1</sup> Jatoi A, Rowland K, Sloan JA, Gross HM, Fishkin PA, Kahanic SP, et al. *Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB)*. Cancer 2008 Aug 15;113(4):847-53 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18543329>.
7. ↑ <sup>7.0</sup> <sup>7.1</sup> Lacouture ME, Mitchell EP, Piperdi B, Pillai MV, Shearer H, Iannotti N, et al. *Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer*. J Clin Oncol 2010 Mar 10;28(8):1351-7 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20142600>.

8. ↑ <sup>8.0</sup> <sup>8.1</sup> Scope A, Agero AL, Dusza SW, Myskowski PL, Lieb JA, Saltz L, et al. *Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption.* J Clin Oncol 2007 Dec 1;25(34):5390-6 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18048820>.
9. ↑ Jatoi A, Thrower A, Sloan JA, Flynn PJ, Wentworth-Hartung NL, Dakhil SR, et al. *Does sunscreen prevent epidermal growth factor receptor (EGFR) inhibitor-induced rash? Results of a placebo-controlled trial from the North Central Cancer Treatment Group (N05C4).* Oncologist 2010;15(9):1016-22 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20798191>.
10. ↑ Bidoli P, Cortinovis DL, Colombo I, Crippa A, Cicchiello F, Villa F, et al. *Isotretinoin plus clindamycin seem highly effective against severe erlotinib-induced skin rash in advanced non-small cell lung cancer.* J Thorac Oncol 2010 Oct;5(10):1662-3 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/20871265>.

[Back to top](#)

## 2.63.4 Appendices

---

[View recommendation components](#)

[View pending evidence](#)

[View body of evidence](#)

[View all comments](#)

[View literature search](#)

[View PICO](#)

[Back to top](#)

## 2.64 Guideline development

---

Guidelines commissioned by

### 2.64.1 Guideline development process

---

#### 2.64.1.1 Introduction

Cancer Council Australia (CCA) was commissioned by Cancer Australia (CA) to revise the treatment section of the Clinical Practice Guidelines for the Diagnosis and Management of Lung Cancer 2004 (Chapters 5 – Management of non-small cell lung cancer and 6 – Management of small cell lung cancer).

The guidelines were developed by a multidisciplinary working group (see Guideline Working Party members). Topic leaders from the Working Party membership were designated to address topics in their areas of expertise, with other Working Group members contributing as co-authors.

The guideline development process, conducting the literature searches, appraising the literature and formulating and grading recommendations, followed the guideline development process outlined below.

[Back to top](#)

### 2.64.1.2 Steps in preparing clinical practice guidelines

A clear strategy was developed and each topic author followed the appropriate steps in preparing their guideline sections. The Working Party developed clinical questions and topic groups were assigned to review and synthesise the relevant literature and to formulate evidence-based recommendations. The search strategy and literature search was conducted by the Project Officer, who distributed the search results to the Working Party authors.

The strategic steps followed are outlined below:

1. Structure the research questions
2. Develop a search strategy
3. Search the literature
4. Critically appraise the literature
5. Formulate and grade recommendations

[Back to top](#)

### 2.64.1.3 Structure the research questions

The Working Party discussed the most important aspects of treatment for non-small cell lung cancer and small cell lung cancer and developed clinically focussed key questions. These questions were developed and approved by Working Party members.

The clinical questions asked for **non-small cell lung cancer and small cell lung cancer**, are as follows:

#### 2.64.1.4 **Non small-cell lung cancer**

##### 2.64.1.4.1 **Stage I operable**

##### 2.64.1.4.2 **Surgery**

- Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage I NSCLC?
- Is minimally invasive lobectomy as effective as open lobectomy for treatment of operable stage I NSCLC?

#### **2.64.1.4.3 Radiotherapy**

- What is the role of radiotherapy in the treatment of operable stage I NSCLC?
- What is the role of radiotherapy after surgery in the treatment of operable stage I NSCLC?

#### **2.64.1.4.4 Chemotherapy**

- What is the role of chemotherapy before surgery in the treatment of operable stage I NSCLC?
- What is the role of chemotherapy after surgery in the treatment of operable stage I NSCLC?

#### **2.64.1.4.5 Stage I inoperable**

##### **2.64.1.4.6 Radiotherapy**

- What is the best practice radiotherapy approach in patients with stage I inoperable NSCLC?

##### **2.64.1.4.7 Surgery**

- What is the role of radiofrequency ablation in stage I inoperable NSCLC?

##### **2.64.1.4.8 Chemotherapy**

- What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage I NSCLC?

#### **2.64.1.4.9 Stage II operable**

##### **2.64.1.4.10 Surgery**

- Does complete mediastinal lymph node dissection improve overall survival compared to mediastinal lymph node staging in stage II NSCLC?

##### **2.64.1.4.11 Radiotherapy**

- What is the role of radiotherapy after surgery in the treatment of operable stage II NSCLC?

##### **2.64.1.4.12 Chemotherapy**

- What is the role of chemotherapy before surgery in the treatment of operable stage II NSCLC?
- What is the role of chemotherapy after surgery in the treatment of operable stage II NSCLC?



### **2.64.1.4.13 Stage II inoperable**

#### **2.64.1.4.14 Radiotherapy**

- What is the best practice radiotherapy approach in patients with stage II inoperable NSCLC?

#### **2.64.1.4.15 Chemotherapy**

- What is the role of chemotherapy when added to radiotherapy in the treatment of inoperable stage II NSCLC?

### **2.64.1.4.16 Stage III operable**

#### **2.64.1.4.17 Radiotherapy**

- What is the role of postoperative radiotherapy (PORT) in resected stage III NSCLC?

#### **2.64.1.4.18 Surgery**

- What is the clinical benefit of mediastinal lymph node dissection in stage IIIA operable NSCLC?
- What is the clinical benefit of the addition of surgery to definitive chemoradiotherapy in stage IIIA (N2) NSCLC?

#### **2.64.1.4.19 Chemotherapy**

- What is the clinical benefit of adjuvant chemotherapy for patients with stage III operable NSCLC?
- What is the clinical benefit of neoadjuvant chemotherapy for patients with stage III operable NSCLC?
- What is the clinical benefit of the addition of neoadjuvant radiotherapy to neoadjuvant chemotherapy in stage IIIA (N2) disease?

### **2.64.1.4.20 Stage III inoperable**

#### **2.64.1.4.21 Radiotherapy**

- What is the recommended treatment approach for the definitive management of patients with good performance status and inoperable stage III disease?
- What is the optimal radiation dose and fractionation schedule for good performance status patients with inoperable stage III NSCLC undergoing curative therapy?
- What are the principles of radiation therapy in the definitive management of stage III inoperable NSCLC?

- What is the optimal treatment approach for patients with stage III inoperable NSCLC who, because of patient or tumour factors, are not suitable for curative treatment with concurrent chemo-radiotherapy?
- What is the role of prophylactic cranial irradiation (PCI) in patients with stage III NSCLC?
- What is the optimal management of Pancoast tumours?

#### **2.64.1.4.22 Stage IV operable**

##### **2.64.1.4.23 Radiotherapy**

- What is the clinical benefit of adjuvant whole brain radiotherapy following resection or stereotactic radiosurgery to the brain metastasis(es)?

##### **2.64.1.4.24 Surgery**

- What is the clinical benefit of video assisted thoracoscopic surgery (VATS) pleurodesis in malignant effusions?
- What is the clinical benefit of resection of brain metastasis?
- What is the clinical benefit of resection of primary disease after complete resection of metastatic disease?

#### **2.64.1.4.25 Stage IV inoperable**

##### **2.64.1.4.26 Radiotherapy**

- What is the clinical benefit of radiotherapy to the lung primary in stage IV NSCLC?
- What is the clinical benefit of radiotherapy to the brain for patients with inoperable brain metastases from NSCLC?
- What is the role of stereotactic radiosurgery in the treatment of brain metastases?
- What is the clinical benefit of radiotherapy to the bone for metastatic disease from NSCLC?
- What is the clinical benefit of radiotherapy in metastatic spinal cord compression?

##### **2.64.1.4.27 Chemotherapy**

- What is the optimal systemic therapy for stage IV inoperable NSCLC?

### **2.64.1.5 Small cell lung cancer**

#### **Limited stage**

#### **2.64.1.5.1 Chemotherapy**

- What is the optimal systemic therapy and duration to be used for the treatment of limited stage small cell lung cancer?
- What is the optimal concurrent chemotherapy to be used for the treatment of limited stage small cell lung cancer with radiotherapy?

#### **2.64.1.5.2 Radiotherapy**

- Which patients with SCLC benefit from prophylactic cranial irradiation?
- What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with limited stage SCLC?
- What is the optimal timing of thoracic radiotherapy in patients receiving chemotherapy for limited stage SCLC?
- What is the optimal dose and fractionation schedule of thoracic radiotherapy in patients with limited stage SCLC?
- What is the optimal treatment volume in patients with limited stage SCLC receiving thoracic radiotherapy?

#### **Extensive stage**

#### **2.64.1.5.3 Chemotherapy**

- What is the optimal chemotherapy regimen and duration of therapy in extensive stage small cell lung cancer in the first-line setting?
- What is the optimal second-line therapy in patients with extensive stage small cell lung cancer?

#### **2.64.1.5.4 Radiotherapy**

- What is the optimal dose and fractionation schedule of prophylactic cranial irradiation in patients with extensive stage SCLC?
- Is there a role for thoracic radiotherapy in patients with extensive stage SCLC?

#### **2.64.1.5.5 Palliative care**

- What is the role of palliative care in symptom management for patients with lung cancer?
- What is the role of advance care planning and timing of referral for patients with lung cancer?
- What is the role of psychological support and interventions in the treatment of lung cancer?

### **2.64.1.5.6 Supportive care**

- What is the role of case management in the treatment of patients with lung cancer?
- What is the role of topical creams, skin moisturisers and maintenance antibiotics in the treatment of rash from anti-EGFR therapy in patients with lung cancer?
- What is the role of early ICC/pleurodesis or early thoracoscopic pleurodesis in the treatment of pleural effusions in patients with stage IV inoperable NSCLC?

[Back to top](#)

### **2.64.1.6 Develop a search strategy**

Appropriate search strategies were constructed for each clinical question. MeSH terms were agreed by the Working Party members and were expanded by the Project Officer after conducting pilot searches and searching the MeSH vocabulary. MeSH index terms were translated to Emtree terms for the Embase database to ensure that appropriate index terms unique to each database were used. When there was no appropriate MeSH or Emtree index term available a combination of free text words were used in order to capture the relevant data.

The following exclusion criteria was applied: studies published pre 2002 (with the exception of some stage III and IV questions and the relevant articles carried on from the 2004 guidelines), languages other than English, and the following study designs: non-systematic reviews, case reports, letters, editorials, comments, animal, in vitro and laboratory studies. The search strategy was approved by the Chair of the Working Party.

[Back to top](#)

### **2.64.1.7 Search the literature**

A range of medical databases, guideline clearinghouses and clinical trial portals were searched. These included The Cochrane Library, PubMed, Embase, Trip Database, the National Guideline Clearinghouse, the National Comprehensive Cancer Network, Canadian Medical Association Clinical Practice Guidelines, the Scottish Intercollegiate Guidelines Network and the National Institute for health and clinical excellence. Search results were screened for relevance by the Project Officer and relevant literature was collated, the full text articles obtained and sent to Working Party topic authors to critically appraise, synthesise and use as the evidence base for their topic questions.

To view the complete search yield and more detailed information about the literature search such as inclusion and exclusion criteria, please go to each clinical question page. The information can be found in the Appendices on each question page.

[Back to top](#)

### 2.64.1.8 Critically appraise the literature

Relevant articles selected from the literature search were reviewed by the clinical question authors and each article was critically appraised with respect to level of evidence, quality of the evidence, size of the effect and clinical importance and relevance. Level of evidence was assigned according to the following criteria from the NHMRC Evidence Hierarchy:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
<b>I</b>	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
<b>II</b>	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
<b>III-1</b>	A pseudo-randomised controlled trial (i. e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i. e. alternate allocation or some other method)
<b>III-2</b>	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>■ Non-randomised, experimental trial</li> <li>■ Cohort study</li> <li>■ Case-control study</li> <li>■ Interrupted time series with a control group</li> </ul>	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: <ul style="list-style-type: none"> <li>■ Non-randomised, experimental trial</li> <li>■ Cohort study</li> <li>■ Case-control study</li> </ul>

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
<b>III-3</b>	A comparative study without concurrent controls: <ul style="list-style-type: none"> <li>■ Historical control study</li> <li>■ Two or more single arm study</li> <li>■ Interrupted time series without a parallel control group</li> </ul>	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: <ul style="list-style-type: none"> <li>■ Historical control study</li> <li>■ Two or more single arm study</li> </ul>
<b>IV</b>	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.<sup>[1]</sup> ([https://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/developers/nhmrc\\_levels\\_grades\\_evidence\\_120423.pdf](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf))

Back to top

### 2.64.1.9 Formulate and grade recommendations

The body of literature was assessed by each topic author and recommendation grades were assigned using the following criteria adapted from the NHMRC body of evidence matrix:

Component of Recommendation	Recommendation Grade			
	A Excellent	B Good	C Satisfactory	D Poor
		one or two level II studies with low risk of bias or SR/multiple		

Component of Recommendation	Recommendation Grade			
	A Excellent	B Good	C Satisfactory	D Poor
<b>Volume of evidence</b>	several level I or II studies with low risk of bias	level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
<b>Consistency</b>	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
<b>Clinical impact</b>	very large	Substantial	moderate	slight or restricted
<b>Generalisability</b>	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence different to target population but it is clinically sensible to for guideline to apply this evidence to target population	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
<b>Applicability</b>	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.<sup>[1]</sup> ([https://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/developers/nhmrc\\_levels\\_grades\\_evidence\\_120423.pdf](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf))

Recommendation grades are indicated below:

Grade of recommendation	Description
<b>A</b>	Body of evidence can be trusted to guide practice
<b>B</b>	Body of evidence can be trusted to guide practice in most situations
<b>C</b>	Body of evidence provides some support for recommendation(s) but care should be taken in its application
<b>D</b>	Body of evidence is weak and recommendation must be applied with caution

<b>Grade of recommendation</b>	<b>Description</b>
<b>PP</b> (practice point)	Where no good-quality evidence is available but there is consensus among Guideline committee members, consensus-based guidance points are given, these are called "Practice points"

Adapted from: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.<sup>[1]</sup> ([https://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/developers/nhmrc\\_levels\\_grades\\_evidence\\_120423.pdf](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf))

[Back to top](#)

### 2.64.1.10 Write the topic

Topic authors were asked to write the content for their guideline question topic using the following format:

- background
- review of the evidence
- evidence summary with levels of evidence and numbered references
- recommendation(s) and corresponding grade(s)
- references

[Back to top](#)

### 2.64.1.11 Review of the question topics

The body of evidence and recommendations for each question topic were reviewed by the Guidelines Working Party and final recommendations agreed to, based on the evidence.

[Back to top](#)

### 2.64.1.12 Public consultation

The guidelines was released for public consultation to all interested parties in Australia for the period from 1 May to 31 May 2012. The consultation process involved soliciting public review of the draft guidelines through posting onto the Cancer Council Australia Cancer Guidelines Wiki and alerting professional societies and groups and sponsors via link to the site. All feedback on the draft received during the consultation period in Australia was reviewed by the Guidelines Working Party topic authors. Subsequent changes to the draft were agreed by consensus, based on consideration of the evidence.

## 2.64.2 References

<references>

[Back to top](#)



1. ↑ <sup>1.0 1.1 1.2</sup> National Health and Medical Research Council. *NHMRC levels of evidence and grades for recommendations for guideline developers*. Canberra: National Health and Medical Research Council; 2009 Available from: [https://www.nhmrc.gov.au/\\_files\\_nhmrc/file/guidelines/developers/nhmrc\\_levels\\_grades\\_evidence\\_120423.pdf](https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf).

## 2.65 Working party members and contributors

Guidelines commissioned by

### Working party members and contributors

Working party member	Clinical questions
Annabel Pollard RN, BA, Grad. Dip App Psych, M Psych (Clinical) MAPS	
Assoc. Prof. Nick Pavlakis	
Associate Professor Christos Karapetis	
Associate Professor Gavin Wright MD FRACS PhD	
Associate Professor Josephine Clayton MBBS PhD FRACP FACHPM	
Associate Professor Michael Michael MBBS(Hons), BSc (Hons), MD, FRACP	
Associate Professor Shalini Vinod MBBS MD FRANZCR	
Caitlin Broderick	
Di Saward	
Dr Adelaide Morgan	
Dr Alesha Thai	
Dr Dish Herath (Gunawardana)	
Dr Jeremy Ruben MBCh (Hons), FCRadOnc (SA),	

## Clinical practice guidelines for the treatment of lung cancer

Working party member	Clinical questions
FRANZCR, Mmed, MD (Monash)	
Dr Margot Lehman MBBS FRANZCR GDP	
Dr Maria Ftanou BAppSc(Hons) Dpsych Clinical	
Dr Melissa Moore BA BSC MBBS (Hons) FRACP PhD	
Dr Natasha Michael MBChB MRCP MRCGP MSC	
Dr Shawgi Sukumaran	
Dr Stephen Barnett	
Dr Suzanne Kosmider	
Dr Toni Pearson	
Dr Tracy Smith BSc, MBBS, FRACP, Clin Dip Pall Med	
Gary Hammerschlag BSc, MBBS, FRACP	
Mary Duffy	
Matthew Grant MBBS, FRACGP, MBioethics, DipPallMed	
Merlina Sulistio MBBS BMedSc FRACP (palliative medicine)	
Mustafa Khasraw MBChB MD MRCP FRACP	
Prof Matthew Peters MD FRACP	
Professor David Ball MB BS, MD, FRANZCR	
Professor Michael Brown MBBS PhD FRACP FRCPA	

## 2.66 Conflict of interest register

Guidelines commissioned by

### Competing interest declarations

Working party member	Competing interest declaration
Annabel Pollard RN, BA, Grad. Dip App Psych, M Psych (Clinical) MAPS	No competing interest to declare.
Assoc. Prof. Nick Pavlakis	Lung Cancer Advisory Boards: Lilly, Merck-Sereno, Roche, Astra-Zeneca, Boehringer Ingelheim Speaking Honoraria: Lilly, Roche, Merck-Sereno, Pfizer, Boehringer Ingelheim
Associate Professor Christos Karapetis	Advisory Role - Merck, Roche, BMS, Astra Zeneca, MSD Sponsorship to attend Scientific Professional Oncology Society Meetings - Eli Lilly, Roche, Astra Zeneca, BMS, Merck Serono
Associate Professor Gavin Wright MD FRACS PhD	Received an Infrastructure and Educational grant to run a VATS lobectomy course provided by Covidien. Has not received financial benefit personally.
Associate Professor Josephine Clayton MBBS PhD FRACP FChPM	No competing interest to declare.
Associate Professor Michael Michael MBBS(Hons), BSc (Hons), MD, FRACP	No competing interest to declare.
Associate Professor Shalini Vinod MBBS MD FRANZCR	No competing interest to declare.
Caitlin Broderick	To be confirmed
Di Saward	No competing interest to declare.
Dr Adelaide Morgan	To be confirmed
Dr Alesha Thai	To be confirmed
	Received funding from Lilly and Roche to attend scientific meetings.

## Clinical practice guidelines for the treatment of lung cancer

Working party member	Competing interest declaration
Dr Dish Herath (Gunawardana)	Received funding from Roche to conduct a pilot EGFR testing program in patients.
Dr Jeremy Ruben MBBCh (Hons), FCRadOnc (SA), FRANZCR, Mmed, MD (Monash)	No competing interest to declare
Dr Margot Lehman MBBS FRANZCR GDP	No competing interest to declare
Dr Maria Ftanou BAppSc(Hons) Dpsych Clinical	No competing interest to declare.
Dr Melissa Moore BA BSc MBBS (Hons) FRACP PhD	To be confirmed
Dr Natasha Michael MBChB MRCP MRCGP MSC	No competing interest to declare.
Dr Shawgi Sukumaran	To be confirmed
Dr Stephen Barnett	No competing interest to declare
Dr Suzanne Kosmider	Nil
Dr Toni Pearson	To be confirmed
Dr Tracy Smith BSc, MBBS, FRACP, Clin Dip Pall Med	No competing interest to declare
Gary Hammerschlag BSc, MBBS, FRACP	To be confirmed
Mary Duffy	To be confirmed
Matthew Grant MBBS, FRACGP, MBioethics, DipPallMed	To be confirmed
Merlina Sulistio MBBS BMedSc FRACP (palliative medicine)	To be confirmed
Mustafa Khasraw MBChB MD MRCP FRACP	<p>Received sponsorship from Roche, Novartis and Sanofi-Aventis to attend scientific meetings.</p> <p>Received a grant from Merck Serono to conduct a clinical trial.</p> <p>Involved as a consultant and in an advisory capacity by Roche.</p> <p>Nature of input: appraised literature regarding role of chemotherapy in stage IV lung cancer.</p>
Prof Matthew Peters MD FRACP	<p>No competing interest to declare in the currency of the Working Group that are directly relevant to its work in the nominated time span.</p> <p>Received honoraria for CME lectures from AstraZeneca and Boehringer Ingelheim for presentations not related to lung cancer.</p>

Working party member	Competing interest declaration
Professor David Ball MB BS, MD, FRANCR	<p>Sat on Advisory Boards for the following companies during 2010-2011:</p> <p>Lilly Oncology, Boehringer- Ingelheim, Astra Zeneca and Pfizer.</p> <p>Received funding to attend ASCO Chicago 2010 from Boehringer-Ingelheim.</p>
Professor Michael Brown MBBS PhD FRACP FRCPA	<p>Melanoma Advisory Boards for GSK, BMS, and Roche</p> <p>Prostate Cancer Advisory Board for Bayer</p> <p>Research support from Novartis</p> <p>Travel sponsorship from Eli Lilly</p> <p>Educational grant from BMS</p>

## 2.67 Abbreviations

Guidelines commissioned by

### Abbreviations

2G	Second generation
3D	Three-dimensional
3G	Third generation
ACCP	American College of Chest Physicians
ACP	Advance care planning
ADLS	Activities of Daily Living Scale
AI	Angiogenesis inhibitors
ALK	Anaplastic lymphoma kinase
ANITA	Adjuvant Navelbine International Trialist Association
BAE	Bronchial artery embolisation
BED	Biologically equivalent dose
BTS	British Thoracic Society

CAI	Carboxyamino-triazole
CALGB	Cancer and Leukemia Group B trial group
CBT	Cognitive Behaviour Therapy
CHART	Continuous, hyperfractionated, accelerated radiotherapy
CHARTWEL	CHART weekend-less
CI	Confidence intervals
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPR	Cardio pulmonary resuscitation
CRT	Chemoradiotherapy
CT scan	Computed tomography scan
CTV	Clinical Target Volume
DRR	Digitally reconstructed radiographs
DVHs	Dose volume histograms
EBUS	Endo bronchial ultrasound
EML4	Echinoderm microtubule-associated protein-like 4
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal growth factor receptor
ENI	Elective nodal irradiation
EORTC	European Organisation for Research and Treatment of Cancer
FEV1	Forced expiratory volume in one second
FIS	Functional independent survival
FNA	Fine needle aspiration
GA	General anaesthesia
GTV	Gross Tumour Volume
HART	Hyperfractionated accelerated radiotherapy
HR	Hazard ratio
HRQOL	Health-related quality of life
HVLT	Hopkins Verbal Learning Test
IALT	International Adjuvant Lung cancer Trial
ICC	Intercostal catheter
IFRT	Involved field radiotherapy

IHC	Immunohistochemistry
IMRT	Intensity-modulated radiation therapy
LACE	Lung adjuvant cisplatin evaluation
LCNS	Lung Cancer Nurse Specialist
LUNG ART	Lung Adjuvant Radiotherapy Trial
MAb	Monoclonal antibody
MCGP	Meaning Centered Group Psychotherapy
MIR	Morphine Immediate release
MLD	Mean total lung dose
Mm/r	Morphine Modified release
MMPs	Matrix metalloproteinases
MMSE	Mini-mental status examination
MPE	Malignant pleural effusion
MRI	Magnetic resonance imaging
NCCTG	North Central Cancer Treatment Group
NNH	Number needed to harm
NNT	Number needed to treat
NSAIDS	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OS	Overall survival
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PET scan	Positron emission tomography
PFS	Progression free survival
PORT	Postoperative external beam radiotherapy
PS	Performance status
PTV	Planning Target Volume
QALY	Quality Adjusted Life Years
QOL	Quality of life
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
RCT	Randomised controlled trial
RFA	Radiofrequency ablation
RR	Relative risk or Response rate

RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic ablative radiotherapy
SCC	Squamous cell carcinoma
SCLC	Small cell lung cancer
SCLC-LS	Small cell lung cancer - limited stage
SCLC-ES	Small cell lung cancer - extensive stage
SEER	Surveillance, Epidemiology and End Results
SGP	Supportive group psychotherapy
SMD	Standardised mean difference
SRS	Stereotactic radiosurgery
TAE	Transcatheter arterial embolisation
TKIs	Tyrosine kinase inhibitors
TPC	Tunnelled pleural catheter
VAS	Visual analogue scale
VATS	Video-assisted thoracic surgery
VEGF	Vascular endothelial growth factor
WBRT	Whole brain radiotherapy