Cancer Council Australia

Clinical practice guidelines for the treatment of lung cancer

Guidelines commissioned by

1 Clinical practice guidelines for the treatment of lung cancer

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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 67 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.[1] 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).[2] 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 113 recommendations and 72 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, FRANCZR

Chair, Lung Cancer Guidelines Working Party

Peter MacCallum Cancer Centre, Victoria

1.2 References

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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.
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.

2 Summary of recommendations

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

2.2.1 Stage I operable

2.2.1.1 Surgery

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

Recommendation	Grade
	C

Recommendation	Grade
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. Last reviewed November 2015	

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

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

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. Last reviewed December 2015	**B**

2.2.3.1 Radiotherapy

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

Recommendation	Grade
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. Last reviewed December 2015	**D**

Point(s)
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). Last reviewed December 2015

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

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

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

2.2.5.1 Chemotherapy

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

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

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

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

2.2.8 Stage I inoperable

2.2.8.1 Radiotherapy

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

Recommendation	Grade
In patients with inoperable stage I NSCLC and good performance status, high dose radiotherapy is an appropriate treatment option. Last reviewed November 2015	**C**
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. Last reviewed November 2015	**B**

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

2.2.10 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.

Point(s)
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

2.2.10.1 Chemotherapy

2.2.11 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

2.2.12 Stage II operable

2.2.12.1 Surgery

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

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 pathologically confirmed (node positive) stage II NSCLC. Last reviewed November 2015	**B**

2.2.13.1 Radiotherapy

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

Recommendation	Grade
In patients who have had complete resection of stage II NSCLC, postoperative radiotherapy is not recommended. Last reviewed December 2015	**A**

2.2.14.1 Chemotherapy

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

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

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

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

Point(s)
The chemotherapy combination of cisplatin and vinorelbine was the most widely studied regimen which showed benefit. Last reviewed December 2015
There is insufficient evidence to support adjuvant chemotherapy for patients with ECOG performance status of ≥ 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 >5cm 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

2.2.17 Stage II inoperable

2.2.17.1 Radiotherapy

2.2.18 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. Last reviewed November 2015

2.2.18.1 Chemotherapy

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

Recommendation	Grade
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	**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

2.2.20 Stage III operable

2.2.20.1 Radiotherapy

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

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. Last reviewed December 2015	**C**

Point(s)
Post-operative radiation therapy may be considered in the setting of a positive margin. Last reviewed December 2015

2.2.21.1 Surgery

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

Recommendation	Grade
	B

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 pathologically confirmed (mediastinal node positive) stage IIIA NSCLC. Last reviewed November 2015	

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

Recommendation	Grade
Unselected patients with biopsy confirmed stage IIIA (N2) disease are best treated with chemoradiotherapy alone. Last reviewed December 2015	**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

2.2.23.1 Chemotherapy

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

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. Last reviewed December 2015	**A**

Recommendation	Grade
Patients with superior sulcus NSCLC may be considered for induction chemoradiotherapy. Last reviewed December 2015	C

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

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

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. Last reviewed December 2015	C

Point(s)
Surgery alone is not advised in cIIIA (N2) disease.

Point(s)
Last reviewed December 2015

2.2.26 Stage III inoperable

2.2.26.1 Radiotherapy

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

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

Point(s)
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. Last reviewed December 2015
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. Last reviewed December 2015

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

Recommendation	Grade
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. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**B**

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

Recommendation	Grade
Patients can be simulated in the treatment position using an immobilisation device. Last reviewed December 2015	**C**
Treatment planning utilising multi-slice CT image acquisition and a 3D planning system is encouraged. Last reviewed December 2015	**C**
The appropriate window settings may be used when contouring the parenchymal and nodal disease. Last reviewed December 2015	**C**
	B

Recommendation	Grade
Tumour volume delineation may be assisted by the incorporation of FDG-PET information into the CT –based planning system. Last reviewed December 2015	
Tumour volume delineation may be assisted by the use of intravenous contrast during simulation. Last reviewed December 2015	C
The Clinical Target Volume may encompass the Gross Tumour Volume plus a margin of 6-8mm. Last reviewed December 2015	C
Elective nodal irradiation is not recommended. Last reviewed December 2015	C

Point(s)
Treatment planning may utilise an accepted method of evaluating and accounting for tumour motion. Last reviewed December 2015
Individual characteristics of breathing and variations associated with tumour location and pulmonary and tumour pathology lead to individual patterns of tumour motion. Last reviewed December 2015
-The Gross Tumour Volume may encompass the visible disease (both primary and nodal) on CT and/or CT-PET. -The Clinical Target Volume may encompass the Gross Tumour Volume plus a margin to account for microscopic extension of disease .

Point(s)
-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). Last reviewed December 2015
Normal Tissue Dose Volume Constraints 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. Lung: V20 ≤ 30 -35% , Mean total lung dose (MLD) ≤ 20-23Gy A total dose of 50Gy in 2Gy/f to the full spinal cord cross-section is associated with a 0.2% risk of myelopathy. Spinal Cord: 50Gy in 1.8-2.0Gy/f Last reviewed December 2015
A single best threshold volumetric parameter for oesophageal irradiation has not been identified. Last reviewed December 2015

2.2.30 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
The patient's performance status should be taken into consideration when choosing the radiation dose and fractionation pattern: - 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.	**A**

Recommendation	Grade
- Patients with poor performance status should be treated with short courses of treatment. Commonly employed radiotherapy regimens include 10Gy/1f, 16Gy/2f (1f/week). Last reviewed December 2015	
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. Last reviewed December 2015	**A**
For patients with locally advanced, inoperable Stage III NSCLC not fit for curative therapy, consideration should be given to concurrent administration of palliative chemoradiation. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**A**

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

2.2.31 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. Last reviewed December 2015	**B**

2.2.32 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. Last reviewed December 2015	**C**
For patients with unresectable Pancoast tumours and good performance status, the concurrent administration of chemotherapy and radiotherapy is recommended. Last reviewed December 2015	**A**
For patients who have a poor performance status or distant metastatic disease, radiation therapy can be used to palliate symptoms due to Pancoast tumour. Last reviewed December 2015	**C**

2.2.33 Stage IV operable

2.2.33.1 Radiotherapy

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

Recommendation	Grade
Routine adjuvant whole brain radiotherapy is not recommended following surgical resection or radiosurgery for brain metastases. Last reviewed September 2015	**A**

2.2.34.1 Surgery

2.2.35 What is the clinical benefit of resection of brain metastasis?

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. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**C**

Point(s)
Surgery may control symptoms more quickly than WBRT and is reasonable in cases of impending neurological emergency. Last reviewed December 2015
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. Last reviewed December 2015
In cases of multiple metastases, addition of surgery to WBRT may be reasonable for rapid symptom control or for histological confirmation. Last reviewed December 2015
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. Last reviewed December 2015

2.2.36 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

2.2.37 Stage IV inoperable

2.2.37.1 Radiotherapy

2.2.38 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. Last reviewed December 2015	**A**
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. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**B**

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

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.	**C**

Recommendation	Grade
Last reviewed December 2015	
Radiosurgery may be used as an alternative to surgery for patients with one to three brain metastases and stable systemic disease. Last reviewed December 2015	**C**

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

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

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

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.

Point(s)
Last reviewed December 2015

2.2.41 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. Last reviewed November 2015	**B**
Recommended radiotherapy doses for patients treated with radiotherapy alone are 8-20Gy in 1-5 fractions. Last reviewed November 2015	**B**

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

2.2.41.1 Chemotherapy

What is the optimal first-line chemotherapy regimen in patients with stage IV inoperable NSCLC? - currently being updated Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC? - currently being updated

2.2.42 Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC?

Recommendation	Grade
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. Last reviewed September 2017	**A**
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. Last reviewed September 2017	**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. Last reviewed September 2017	**B**

Point(s)
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. Last reviewed September 2017

2.2.43 Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC?

Recommendation	Grade
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. Last reviewed September 2017	**A**
Patients unfit for combination chemotherapy could be considered for 3G monotherapy with vinorelbine, paclitaxel, docetaxel or gemcitabine. Last reviewed September 2017	**A**

Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC? - currently being updated Are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens for treatment of stage IV inoperable NSCLC? - currently being updated

2.2.44 What is the optimal duration of first-line chemotherapy for treatment of stage IV inoperable NSCLC?

Recommendation	Grade
First-line combination chemotherapy should in most cases be stopped at disease progression or after four cycles in patients with advanced NSCLC. Last reviewed September 2017	**B**

Point(s)
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.

Point(s)
Last reviewed September 2017

Is chemotherapy with a biologic or targeted therapy superior to chemotherapy alone in unselected patients for treatment of stage IV inoperable NSCLC? - currently being updated

2.2.45 What is the optimal chemotherapy regimen for overall quality of life for patients in the treatment of stage IV inoperable NSCLC?

Point(s)
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. Last reviewed September 2017

2.2.46 What is the optimal first-line maintenance therapy for treatment of stage IV inoperable NSCLC?

Recommendation	Grade
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 for delaying tumour progression in unselected patients, include docetaxel, whilst in patients with non-squamous cell carcinoma histology, pemetrexed. Options most proven for prolongation of survival is pemetrexed. Last reviewed September 2017	**A**
Pemextrexed in stage IV non-squamous NSCLC should be considered for maintenance therapy. Last reviewed September 2017	**B**

What is the optimal second-line therapy in patients with stage IV inoperable NSCLC? - currently being updated What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC? - currently being updated

2.2.47 What is the optimal systemic therapy regimen for patients with poor performance status for treatment of stage IV inoperable NSCLC?

Recommendation	Grade
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. Last reviewed September 2017	**B**
Poor performance status patients having received 1 or 2 lines of prior therapy, may be offered erlotinib 150 mg daily. Last reviewed September 2017	**B**

Point(s)
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. Last reviewed September 2017

2.2.48 What is the optimal systemic therapy regimen for elderly patients for treatment of stage IV inoperable NSCLC?

Recommendation	Grade
Suitably fit patients over 65 years of age, can be offered first-line mono-chemotherapy with a 3G single agent (vinorelbine (25-30 mg/ m2 day one, eight Q3 weekly), docetaxel (60 mg/m2 day one, Q3 weekly) or gemcitabine (1150 mg /m2 days one and eight, Q3 weekly). Last reviewed December 2015	**B**

Recommendation	Grade
In elderly patients, first-line gemcitabine doublet chemotherapy is not recommended. Last reviewed December 2015	**B**
In fit elderly patients, first-line carboplatin/weekly paclitaxel may be offered instead of 3G monotherapy, but at the expense of greater neutropaenia. Last reviewed December 2015	**B**

What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC? - currently being updated

2.3 Small cell lung cancer

2.3.1 Limited stage

2.3.1.1 Chemotherapy

2.3.2 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**
Therapy beyond the standard four cycles of induction chemotherapy cannot be recommended. Last reviewed November 2015	**A**

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

2.3.3 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. Last reviewed August 2015	**B**

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

2.3.3.1 Radiotherapy

2.3.4 Which patients with SCLC benefit from prophylactic cranial irradiation?

Recommendation	Grade
Patients with limited stage and a complete response to initial therapy, and patients with extensive stage andstage who do not receive MRI brain and any response to initial therapy, should be offered prophylactic cranial irradiation.	**A**

Recommendation	Grade
Last reviewed September 2017	

Point(s)
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. Last reviewed September 2017
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. Last reviewed September 2017

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

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. Last reviewed September 2017	**B**

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

Recommendation	Grade
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. Last reviewed September 2017	**B**

Point(s)
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. Last reviewed September 2017

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

Recommendation	Grade
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. Last reviewed August 2017	**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

Point(s)
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

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

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. Last reviewed September 2017	**B**
Elective nodal irradiation may be omitted to reduce toxicity. Last reviewed September 2017	**C**

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. Last reviewed September 2017

2.3.9 Extensive stage

2.3.9.1 Chemotherapy

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

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. Last reviewed December 2015	**B**

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 aditional benefit. Last reviewed December 2015

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

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). Last reviewed December 2015	**A**

2.3.11.1 Radiotherapy

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

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. Last reviewed November 2015	**B**

Point(s)
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. Last reviewed November 2015

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

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

Point(s)
Chest radiotherapy was administered 6-7 weeks after chemotherapy and usually 1 week after completion of prophylactic cranial irradiation.

Point(s)
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. Last reviewed December 2015

2.4 Palliative care

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

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. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**B**
The use of opioids are recommended for the relief of dyspnoea in patients with NSCLC. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**B**

Recommendation	Grade
Subcutaneous methylnaltrexone should be considered in patients where conventional laxatives have failed. Last reviewed December 2015	**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. - 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 mucopurulant sputum.

Point(s)
-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
It is recommended to refer patients with stage IV inoperable NSCLC to palliative care at the time of diagnosis of metastatic disease. Last reviewed December 2015	**B**
Advance care planning discussions should be initiated with patients, as there are multiple benefits. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**C**

Point(s)
Consider referral to palliative care when metastatic disease is diagnosed. Don't wait until there is definite evidence of medical deterioration. Last reviewed December 2015

Point(s)
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. Last reviewed December 2015

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

Recommendation	Grade
Psycho-educational interventions including: counseling, behaviour therapy, education/information giving, and social support will assist in ameliorating the impact of depression. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**B**
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. Last reviewed December 2015	**B**
	C

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. Further randomised controlled trials involving adequately powered studies and consistent methodology can be conducted to ascertain unmet needs in advanced cancer. Last reviewed December 2015	
Psychological interventions have an important role in the management of cancer related pain. Last reviewed December 2015	**B**
Quality of life of lung patients may improve with behavioural, cognitive or social cognitive therapies. Last reviewed December 2015	**C**
Non-invasive nurse-led programs with a focus on managing physical symptoms and treatment related toxicities may be used to optimise quality of life. Last reviewed December 2015	**C**

2.5 Supportive care

2.5.1 What is the optimal management of malignant pleural effusions?

Recommendation	Grade
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.	**B**

Recommendation	Grade
Last reviewed January 2017	
Indwelling pleural catheters might be effective in the outpatient management of malignant pleural effusion. Last reviewed January 2017	**C**
Consider the use of an Indwelling pleural catheter in malignant pleural effusion caused by Haematological malignancies Last reviewed January 2017	**D**
VATS talc pleurodesis is recommended in fit (ECOG 0-2) patients with NSCLC with an expected survival of >2 months who have >90% lung expansion after needle thoracocentesis. Last reviewed January 2017	**A**
VATS talc pleurodesis may be considered in fit (ECOG 0-2) patients with NSCLC with an expected survival of >2 months who have <90% lung expansion after needle thoracocentesis. VATS with biopsy and subsequent talc pleurodesis may be considered in patients who require pathological confirmation of their cancer to determine management. Last reviewed January 2017	**C**
Intrapleural Hyperthermic Perfusion Chemotherapy (HIPEC) could be used in the treatment of malignant pleural effusions. Last reviewed January 2017	**C**
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. Last reviewed January 2017	**A**
Consider the use of radiofrequency ablation in addition to thoracoscopic pleurodesis in MPE from NSCLC for improved survival. Last reviewed January 2017	**D**

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

Point(s)
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

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

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. Last reviewed October2015	**B**

Point(s)
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. Last reviewed October2015

Point(s)
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. Last reviewed October2015
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. Last reviewed October2015

2.5.3 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. Last reviewed September 2017	**C**

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.

Point(s)
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
Topical formulations of steroids and tacrolimus do not add to the benefit of antibiotic treatment. Last reviewed September 2017
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. Last reviewed September 2017
Patients with clinically significant rash may be commenced on oral antibiotic therapy with tetracycline, minocycline or doxycycline. Last reviewed September 2017
The treatment for paronychia is based on expert opinion as no randomised controlled trials have evaluated the therapies. 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.

Point(s)
In severe cases and signs of infection, it is recommended to swab, treat with appropriate systemic antibiotic and refer to dermatologist. Last reviewed September 2017

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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
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP (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.[1] (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[1]:

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	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
II	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
III-1	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)
III-2	A comparative study with concurrent controls: ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study ■ Interrupted time series with a control group	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: ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
III-3	A comparative study without concurrent controls: ■ Historical control study ■ Two or more single arm study ■ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ■ Historical control study ■ Two or more single arm study
IV	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)

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2.1 Complete lymph node dissection vs lymph node staging

Contents

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.

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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[1], the completion of a large randomised controlled trial by the American College of Surgeons Oncology Group[2], 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[3]. A systematic review and meta analysis confirmed the lack of survival benefit of complete mediastinal lymph node dissection over systematic mediastinal lymph node sampling.[4]

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2.1.2 Evidence summary and recommendations

Evidence summary	Level	References
	I, II	[2], [3], [4]

Evidence summary	Level	References
Complete mediastinal lymph node dissection does not improve survival for patients having surgical resection for pathologically proven stage I NSCLC. Last reviewed November 2015		

Evidence-based recommendation	Grade
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. Last reviewed November 2015	**C**

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. Last reviewed November 2015

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2.2 Minimally invasive lobectomy vs open lobectomy

Contents

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[1]. 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.[2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24]

Evidence from a further small randomised controlled trial[25] 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.

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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. Last reviewed December 2015	III-1, III-2	[1], [2], [3], [4], [5]
Minimally invasive lobectomy may be superior to open lobectomy with respect to reported post-operative complication rates.	II, III-2	[2], [4], [5], [25]

Evidence summary	Level	References
Last reviewed December 2015		

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. Last reviewed December 2015	**B**

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2.3 Radiotherapy

Contents

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.

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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 ($P<0.0001$).[1]

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2.3.1.3 Surgery versus conventional radiotherapy

There has been no modern randomised comparison of surgery with conventional fractionated radiotherapy in patients with operable disease. In a population-based study using results from the North American Surveillance Epidemiology and End Result (SEER) database, the survival of patients having surgery was compared with that

of patients treated with radiotherapy, including patients who were eligible to have surgery but refused.[2] The type of radiotherapy was not described, but around half the patients were treated in the period (1988-2002) before the use of SABR for stage I NSCLC became widespread. Patients who had surgery had superior survival compared with those who refused it with a hazard ratio of 0.437 (95% C.I. 0.301-0.632). In a further analysis of the SEER database 2001-2007, restricted to patients over the age of 65, survival following conventional radiotherapy was significantly worse than for patients having lobectomy or sublobar resection.[3]

In a single institution study, survival was better for patients with high risk stage I NSCLC having limited resection versus 3D conformal radiotherapy.[4] This difference was no longer evident after a multivariate analysis including other prognostic factors, or after a propensity-matched analysis of 34 matched pairs. In another single institution study the local control and survival at three years were 76% and 63% respectively for 40 patients having surgery, and 78% and 55% for 39 patients having conventionally fractionated radiotherapy.[5]

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2.3.1.4 Surgery versus SABR

Two randomised trials (ROSEL and STARS) in which surgery was compared with SABR in patients with operable clinical stage I NSCLC were closed early because of slow accrual.[6] Data from the two trials were pooled and survival based on intention- to- treat was compared between the arms. It should be noted that although survival was the primary endpoint in the STARS trial, it was an *a priori* defined secondary endpoint in the ROSEL trial. In ROSEL, the primary endpoints were local and regional control. Thirty one patients were randomised to SABR and 27 to surgery. The estimated overall survival at three years was 95% (95% C.I. 85-100) in the SABR group and 79% (95% C.I. 64-97) in the surgery group, with a hazard ratio of 0.14 (95% C.I. 0.017-1.190), p=0.037. There were no significant differences in recurrence free survival between the groups. Six patients died during follow up in the surgery group (two from cancer progression, one from second primary lung cancer, one from a surgical adverse event, and two from comorbidities). One patient in the SABR group died from cancer progression. Not all patients in the ROSEL study had pathologic confirmation of NSCLC. Of the six patients without a preoperative diagnosis on the surgical arm, one proved to have benign disease. Eight patients on the radiotherapy arm had no pathologic confirmation. The authors concluded that “SABR could be an option for treating operable stage I NSCLC. Because of the small sample size and short follow up, additional randomised studies are warranted.”

There are a number of non-randomised studies comparing outcomes in patients receiving surgery versus outcomes in patients receiving SABR for stage I NSCLC. Usually the SABR patients are not fit for surgery and this introduces a bias favouring surgery. In spite of attempts to adjust for differences in prognostic factors between groups, using techniques such as propensity matching and multivariate analysis, the results of these studies are not consistent.

Summary weighted average outcome data from a systematic review of 45 reports of SABR for stage I NSCLC comprising 3201 patients revealed a two year survival of 70% (95% C.I. 67-72).[7] This was similar to the 68% survival at two years (95%C.I. 66-70) for patients treated with surgery on a separate database from an earlier time period. Two year weighted average local control following SABR based on data from 29 studies in which it was reported was 91% (95% C.I. 90-93). These outcomes were not adjusted for comorbidity or other prognostic factors.

Although described as a meta-analysis, the study of Zheng et al is a comparison of outcomes reported in single arm SABR cohort studies versus outcomes in single arm surgery cohort studies from the same time period.[8] After adjusting for the effects of age and operability, there were no differences in overall survival comparing SABR with lobectomy (HR = 0.52, 95% C.I. 0.20-1.36, P = 0.15) or SABR with sublobar resection (HR = 0.49, 95% C.I. 0.19-1.30, P = 0.18).

Two population based studies using SEER data have compared outcomes in older patients (66 years and over) having surgery or SABR. In the first study (2001-2007), there was no significant difference in survival between 99 propensity matched pairs of patients having lobectomy or SABR with HR = 0.71 (95% C.I. 0.45-1.12, P = 0.14).[3] In the second study (2007-2009) survival and toxicity were compared in propensity score matched patients undergoing SABR (n=367) or lobectomy/sublobar resection (n=711).[9] Overall mortality was lower with SABR at 3 months (2.2% vs 6.1%, P = 0.005), but at 24 months it was higher (40.1% vs 22.3%, P < 0.001). Acute toxicity in the first month was lower with SABR (7.9% vs 54.9%, P < 0.001), but at 24 months there were no differences between treatments.

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).[10]

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%.[11]

Institution-based studies comparing SABR with surgery are usually small and underpowered, especially after propensity-score based matching. Some report a survival advantage for surgery patients[12][13][14] and others no difference after adjusting for prognostic factors.[15][16][17][18]

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2.3.1.5 Surgery or SABR for patients unsuitable for lobectomy

There has been no direct comparison of segmentectomy or wedge resection versus radiotherapy. There are three retrospective non-randomised studies which have reported local control and survival following limited surgery or SABR in patients unsuitable for lobectomy.

In the first study, which used data from the SEER 2001-2007 cohort, there were no survival differences between 112 propensity score based matched pairs having sublobar resection or SABR (HR = 0.82, 95% C.I. 0.53-1.27, P = 0.38).[3]

In the second study, unadjusted survival was superior in patients having wedge resection compared with SABR.[19]

The third study, from Japan, reported no significant differences in survival between sublobar resection and SABR after propensity score matching.[20]

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2.3.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients with operable stage I NSCLC, surgery is associated with superior survival compared with conventionally fractionated radiotherapy. Last reviewed December 2015	III-2	[3]
In patients with operable stage I NSCLC, SABR may be associated with similar survival compared with surgery in the medium term. Last reviewed December 2015	II	[6]

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**D**

Practice point

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).

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2.4 Radiotherapy after surgery

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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.[1][2]

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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.[3]

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.

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2.4.1.3 Brachytherapy in addition to sublobar resection

Since local recurrence is more frequent after sublobar resection compared with lobectomy,[4] the American College of Surgeons Oncology Group (ACOSOG) conducted a randomised trial of sublobar resection with and without I-125 seed brachytherapy in patients with high risk stage I NSCLC. The addition of brachytherapy did not affect local recurrence, morbidity or survival.[1][2]

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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. Last reviewed December 2015	I	[3]
The use of I-125 seed brachytherapy applied to the tumour bed after sublobar resection for high risk stage I NSCLC does not improve local recurrence rates or survival. Last reviewed December 2015	II	[2]

Evidence-based recommendation	Grade
In patients who have had complete resection of stage I NSCLC, postoperative radiotherapy is not recommended. Last reviewed December 2015	**A**

Evidence-based recommendation	Grade
I-125 seed brachytherapy to the tumour bed is not recommended after sublobar resection for stage I NSCLC. Last reviewed December 2015	**B**

Practice point
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

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2.5 Chemotherapy before surgery

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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.

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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.[1] 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.[2] An associated systematic review did reveal a benefit.[3] 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.[4] A previous systematic review produced similar conclusions.[5] 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.[6] 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.[7]

Brouchet et al[8] 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.[9]

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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. Last reviewed December 2015	I, II	[7], [6], [1]

Evidence-based recommendation	Grade
Neoadjuvant chemotherapy is not considered standard therapy for stage IA NSCLC. Last reviewed December 2015	**B**

Evidence summary	Level	References
There is insufficient data to support the administration of chemotherapy before surgery for stage IB NSCLC. Last reviewed December 2015	I, II	[7], [6], [1]

Evidence-based recommendation	Grade
Neoadjuvant chemotherapy is not considered standard therapy for stage IB NSCLC. Last reviewed December 2015	**B**

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2.6 Chemotherapy after surgery

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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 aminopeptoidase inhibitor specifically for stage I NSCLC of squamous cell histology.[1] 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. Burdett et al have performed an individual patient data meta-analysis as part of a Cochrane Review. 414 patients with stage IA disease were included in this analysis from trials that evaluated platinum based adjuvant chemotherapy. 1644 stage IA patients came from studies that evaluated UFT/Tegafur. This meta-analysis could not demonstrate a convincing survival benefit for adjuvant chemotherapy when used as part of the treatment of stage 1A NSCLC. [2]

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2.6.1.2 Post-operative adjuvant chemotherapy for stage IB

As above, several trials from Japan have demonstrated a benefit for Tegafur- Uracil,[3][4] and another study from Japan showed a benefit with bestatin.[1] 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. An individual patient data meta-analysis as part of a Cochrane Review did demonstrate a survival benefit for adjuvant chemotherapy after surgery for stage 1B NSCLC, with an estimate of the absolute benefit measuring 5%. [2]. This analysis included data from 3005 patients, the majority include in trials that

evaluated platinum based chemotherapy regimens as adjuvant therapy. 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.[5] A retrospective analysis from the National Cancer Database in the USA revealed a low utilisation of adjuvant chemotherapy in stage I NSCLC, but those that received adjuvant chemotherapy had a better survival. The survival benefit was also demonstrable in patients with tumours that were less than 4 cm in size, [6]

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.[7] 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.[8] 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.[9] A Quality of Life analysis from JBR.10 did reveal maintenance of QoL for the majority of patients on adjuvant chemotherapy.[10] 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 (p=0.07), indicating that the benefit associated with adjuvant chemotherapy did not differ in patients with stage IB NSCLC. [11]

Long-term data from the International Adjuvant Lung Cancer Trial (IALT) revealed that adjuvant chemotherapy reduced the risk of local cancer recurrence and non-brain metastases, but it id not reduce the rate of brain metastases. Whilst cancer recurrence and cancer related death was reduced, there was an observed increase in non-cancer related deaths seen after 5 years of follow up. The authors postulated that the deaths may be attributable to the late effects of cisplatin, but the observed benefit of adjuvant chemotherapy in related to reducing cancer deaths outweighed the numerically low non-cancer deaths ([12])

The largest and most contemporary meta-analysis has demonstrated a 5% survival benefit in favour of adjuvant chemotherapy for the treatment of stage IB disease [2]. This meta-analysis included individual patient data form all the eligible trials that compared chemotherapy versus no chemotherapy. Another meta-analysis, this type using summary statistics from the included trials and not IPD, examined stage IB NSCLC only and included 4656 patients from 16 eligible trials. This also reported a survival benefit with adjuvant chemotherapy, but the benefit was restricted to those that received more than 4 cycles of cisplatin based chemotherapy or Tegafur [13] A meta-analysis using individual patient data from four of the largest RCTs showed a benefit, but subgroup analysis suggested the benefit was restricted to stage II and III.[14] 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.[15] A small randomized phase II study from Italy did support a benefit in stage IB disease using cisplatin and etoposide.[16] An EORTC study showed no benefit for stage I-III NSCLC with adjuvant MVP – mitomycin, vinblastine and cisplatin.[17] 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 addressed the question of the role of combined chemotherapy and radiotherapy given in the adjuvant setting. Twelve trials were included that compared adjuvant chemo-radiation versus adjuvant irradiation alone. In 9 studies the chemotherapy was given before the radiotherapy and in 4 studies the chemotherapy and the radiotherapy were administered concurrently (for 1 study both pre RT chemotherapy and concurrent CRT was administered). A total of 2660 patients were included. For cisplatin-based combination chemotherapy there was a benefit of 4% in absolute survival at five years, increasing from 29 to 33% (p=0.009). [2]

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. Last reviewed December 2015	I	[1], [3], [18], [5], [7], [8], [9], [10], [11], [15], [16], [17], [2]

Evidence-based recommendation	Grade
Post-operative adjuvant chemotherapy is not recommended for stage IA NSCLC. Last reviewed December 2015	**B**

Evidence summary	Level	References
Platinum-based adjuvant chemotherapy for patients with stage IB NSCLC is associated with a survival benefit. Meta-analyses reveal an absolute survival benefit of 5%. The benefit is observed in tumours that are greater than 3-4 cm in maximal diameter. Last reviewed December 2015	I	[1], [3], [18], [5], [7], [8], [9], [10], [11], [15], [16], [17], [2], [12], [13], [6]

Evidence-based recommendation	Grade
Platinum-based adjuvant chemotherapy is recommended for all patients with stage IB NSCLC.	**B**

Evidence-based recommendation	Grade
Last reviewed December 2015	

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2.7 Radiotherapy best practice

Contents

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

2.7.1.1 Background

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.[1] 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. A randomised phase 3 trial of conventional radiotherapy (55 Gy in 20 fractions) with and without concomitant gemcitabine in patients with stage I and II NSCLC was closed early because of slow accrual.[2] There were no differences in survival between arms but significantly more adverse events in patients randomised to gemcitabine.

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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.[3]

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.[1] 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.[4] 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. A more convenient method of accelerating radiotherapy by giving larger doses per fraction once a day over three weeks was investigated in a Canadian phase II trial NCIC BR.25.[5] The schedule under investigation (60 Gy in 15 fractions) resulted in a primary tumour control rate of 87% at 2 years without excessive toxicity in patients with peripheral stage I NSCLC. Although promising, direct comparison with more widely used schedules is lacking.

There are no randomised studies directly comparing the effect of increased radiation dose 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).[6][7] However, fatal toxicity has been reported following SABR, particularly for centrally located and larger tumours.[6] As a result, only peripheral tumours 5 cm or less in diameter were included in the RTOG 0236 phase II trial of SABR for NSCLC.[7]

In a retrospective study using the North American Surveillance, Epidemiology and End Results (SEER) database, the outcomes in 124 propensity-matched pairs of patients having SABR or conventional radiotherapy were compared.[8] Survival favoured the SABR patients, with an HR = 1.97 (95% C. I. 1.31-2.96, P = 0.001). A small retrospective single institution study revealed no differences in primary tumour control and survival between patients treated with conventional fractionation or SABR.[9] It seems reasonable to conclude, based on the limited low level evidence, that SABR is not inferior to conventionally fractionated radiotherapy, but more convenient for the patient and less demanding of resources. 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”.[10]

In the case of SABR, there is little evidence to recommend one dose fraction schedule over another. NRG Oncology’s RTOG 0915 was a randomised phase II trial comparing a single dose of 34 Gy with 48 Gy in 4 fractions in stage I NSCLC.[11] The intent was to determine which regimen resulted in the lower rate of adverse events without a reduction in local primary tumour control. There was no significant difference between treatments in adverse events, and primary control at one year was 97% for the single dose and 93% for the four fractions. The authors concluded that the single dose was worthy of further investigation.

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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. Last reviewed November 2015	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. Last reviewed November 2015	**C**

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. Last reviewed November 2015	II	[3]
Shortening overall radiotherapy treatment time may improve local control and survival. Last reviewed November 2015	II	[1], [4]

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. Last reviewed November 2015	**B**

Practice point
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

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2.8 Radiofrequency ablation

Contents

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.

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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.[1] 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.[2] There were three cases of pneumothorax requiring therapy in patients having RFA, but none in the other groups. A third non-randomised study, with only 22 patients, reported longer survival in matched patients treated with surgery compared with RFA (P = 0.054).[3] In a larger single institution cohort study, survival (not adjusted for risk factors) was superior in high risk patients having wedge resection (n = 59) compared with RFA (n = 62), P = 0.044, but when the analysis was restricted to patients with T1 tumours, the difference was no longer significant (P = 0.499).[4] Finally, in a single institution retrospective comparison of primary tumour control and survival in patients with stage I NSCLC who were treated with sublobar resection, RFA or radiotherapy (both conventional fractionation and SABR), primary tumour control was superior in patients having sublobar resection compared with the other modalities, but there were no differences in overall survival.[5]

In a non-randomised single institution study, the survival and cost of treating elderly patients unsuitable for lobar resection were compared for sublobar resection (n = 28) and RFA (n = 56). In addition to the primary therapies, there were differences in the use of adjuvant chemotherapy and radiotherapy between the groups. Although the survival of the surgical group was significantly longer, the cost per month of life lived was less for the RFA group.[6]

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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.

Last reviewed December 2015

Practice point

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

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2.8.3 References

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2.9 Radiotherapy plus chemotherapy

Contents

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.[1] 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.[2][3] 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.

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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.

Last reviewed December 2015

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2.9.3 References

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2.10 Complete lymph node dissection vs lymph node staging

Contents

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.

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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[1], it was found that the evidence already existed for a survival benefit from complete mediastinal lymph node dissection. This was specifically reported in 2006[2], but did not generate the level of interest that accompanies new pharmacological interventions. The randomised trials by Wu et al[3] and Passlick et al[4] 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[5], that it could be inferred that the benefit of complete mediastinal dissection is clearest in stage II and higher NSCLC. A further systematic review and meta analysis by Huang et al[6] included patients with all stages of NSCLC and found no difference in overall survival between complete mediastinal lymph node dissection and systematic lymph node sampling. However this analysis was heavily weighted towards very early pathologic Stage I patients by inclusion of the ACOSOG Z30 trial.[5]

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2.10.2 Evidence summary and recommendations

Evidence summary	Level	References
Complete mediastinal lymph node dissection may be associated with improved overall survival compared to lymph node staging alone in patients with unknown stage or stage II-III NSCLC. Last reviewed November 2015	I, II	[1], [4], [2], [3], [6]

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 pathologically confirmed (node positive) stage II NSCLC. Last reviewed November 2015	**B**

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2.10.3 References

1. ↑ [1.0] [1.1] 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.
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2.11 Radiotherapy after surgery

Contents

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.

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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. [1]

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.

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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 Last reviewed December 2015	I	[1]

Evidence-based recommendation	Grade
In patients who have had complete resection of stage II NSCLC, postoperative radiotherapy is not recommended. Last reviewed December 2015	**A**

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2.11.3 References

1. ↑ [1.0] [1.1] 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.

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2.12 Chemotherapy before surgery

Contents

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.

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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[1] 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 where 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,[2] which did not show any significant OS difference in the overall population, while subgroup IB/IIA demonstrated a significant OS benefit. The NATCH trial[3] 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

[4] did not demonstrate any overall survival benefit with neoadjuvant chemotherapy. Neoadjuvant chemotherapy did not have any impact on the quality of life. The FTCG study[5] 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[6] 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[4] 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.[6] A more recent individual patient meta-analysis provides a clearer picture across these studies.[7] This individual patient meta-analysis included 15 randomised controlled trials involving 2385 patients, majority across stages 1B- IIIA. Out of 1194 patients for whom staging information was available, 330 (28%) were stage II patients. A clear overall survival benefit was demonstrated with a HR of 0.87, 95 % confidence interval 0.78-0.96,P=0.007.There was a 13% decrease in relative risk of death with an absolute survival improvement of 5% at 5 years from 40% to 45% overall and 30% to 35% in stage II. This benefit was independent of other variables tested, including chemotherapy regimen, patient demographics and tumour characteristics. There was no demonstrable effect on the operability rate or on the likelihood of achieving a complete resection with administration of chemotherapy before surgery.

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2.12.2 Evidence summary and recommendations

Evidence summary	Level	References
Individual patient meta-analysis shows benefit in overall survival for chemotherapy given before surgery. Last reviewed December 2015	I	[7]
Individual studies looking at chemotherapy use before surgery in stage II disease have inconsistent end points and lack power due to poor accrual and early closure. Last reviewed December 2015	II	[3], [2], [1]
Majority of individual trials do not show statistically significant benefit in stage II disease. Last reviewed December 2015	II	[5], [3], [4], [2]
Chemotherapy given before surgery does not adversely affect the quality of life.	II	[4]

Evidence summary	Level	References
Last reviewed December 2015		
Compliance to chemotherapy given before surgery (neo-adjuvant) is better compared to chemotherapy given after surgery(adjuvant). Last reviewed December 2015	II	[3]
The survival benefits of neoadjuvant chemotherapy are similar whether given before or after surgery. Last reviewed December 2015	I	[6], [8]

Evidence-based recommendation	Grade
Chemotherapy before surgery may be considered as an option for patients with operable stage II NSCLC. Last reviewed December 2015	**B**

Evidence-based recommendation	Grade
Chemotherapy before surgery in operable stage II disease, with 3-4 cycles of platinum-based regimes, may be considered in select patients, who are unlikely to receive it as adjuvant therapy. Last reviewed December 2015	**B**

Practice point
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

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2.12.3 References

1. ↑ 1.0 1.1 Scagliotti GV, Pastorino U, Vansteenkiste JF, Spaggiari L, Facciolo F, Orlowski 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.
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2.13 Chemotherapy after surgery

Contents

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.[1][2][3] 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.

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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[4] 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.[5] 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.[6]

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.[7] However, in an updated publication, with a median follow up of 7.5 years, the survival benefit in favour of chemotherapy became non-significant.[8] 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.[9][10] 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/m2 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.[11] 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)[12]. 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.[13] These results have been further confirmed by an updated individual patient data meta-analysis. An absolute improvement in 5-year survival of 5%, from 40-45%, for stage II disease was again demonstrated. The benefit for chemotherapy was also evident in patients who received adjuvant radiotherapy.[14]

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.[15] These tumours would be classified under IIA in the 7th edition of TNM classification.These groups of patients also may benefit from adjuvant chemotherapy as evidenced by updated meta-analysis data.[14]

There is limited evidence on the long term toxicities of adjuvant chemotherapy. An updated analysis of the IALT study with a follow up of 7.5 years confirmed a benefit of adjuvant chemotherapy within the first 5 years. However after that period there was an increased risk of non-cancer mortality in the group who received chemotherapy (HR 3.6; 95% CI 2.2-5.9, p< 0.001).[16] However this affected only about 2% of the study population. These results need further validation from long term follow up results of similar studies.

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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 cisplatin-based chemotherapy after surgery Last reviewed December 2015	I, II	[11], [6], [17], [5], [7], [8], [10], [12], [18], [9], [19]
The benefit of chemotherapy after surgery is present in patients who received radiotherapy as part of the loco-regional treatment. Last reviewed December 2015	I	[14]

Evidence-based recommendation	Grade
Patients with completely resected stage II NSCLC should be offered 3-4 cycles of adjuvant cisplatin based chemotherapy. Last reviewed December 2015	**A**

Practice point
The chemotherapy combination of cisplatin and vinorelbine was the most widely studied regimen which showed benefit. Last reviewed December 2015

Practice point

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

Last reviewed December 2015

Practice point

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

Last reviewed December 2015

Practice point

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

Last reviewed December 2015

Practice point

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

Practice point

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

Last reviewed December 2015

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2.13.3 References

1. ↑ Ponn RB, Lo Cicero J III, Rusch VW. *BDT: Surgical treatment of nonsmall 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.
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15. ↑ .
16. ↑ Rotolo F, Dunant A, Le Chevalier T, Pignon JP, Arriagada R, IALT Collaborative Group. *Adjuvant cisplatin-based chemotherapy in nonsmall-cell lung cancer: new insights into the effect on failure type via a multistate approach.* Ann Oncol 2014 Nov;25(11):2162-6 Available from: http://www.ncbi.nlm.nih.gov /pubmed/25193990.
17. ↑ .
18. ↑ .
19. ↑ .

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2.14 Radiotherapy best practice

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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;[1] in the CHARTWEL study, it was 6%.[2] A randomised phase 3 trial of conventional radiotherapy (55 Gy in 20 fractions) with and without concomitant gemcitabine in patients with stage I and II NSCLC was closed early because of slow accrual.[3] There were no differences in survival between arms but significantly more adverse events in patients randomised to gemcitabine. Because of the paucity of evidence for inoperable node positive stage II disease, it seems reasonable to use the recommendation guidelines for node positive 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 with or without concomitant chemotherapy.

Last reviewed November 2015

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2.14.3 References

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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.
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2.15 Radiotherapy plus chemotherapy

Contents

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.

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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,[1] 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[2] 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.

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2.15.1.3 Concurrent versus sequential therapy

In a meta-analysis of concomitant versus sequential radio-chemotherapy,[3] 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.

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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. Last reviewed August 2015	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. Last reviewed August 2015	**C**

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. Last reviewed August 2015

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2.16 Radiotherapy after surgery

Contents

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.[1] 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.[2] However, the effect of adjuvant chemotherapy on loco-regional control is not clear.

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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

2.16.2.1 Post-operative Radiotherapy

The use of radiotherapy (RT) post surgical resection reduces the risk of local recurrence.[3][4][5][6] 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%).[7] 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.[8] 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.[9] 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. 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.

A population-based study using the National Cancer Database, identified 3340 patients treated with PORT using modern radiation therapy techniques between 1998-2006. PORT resulted in a statistically significant reduction in 5 year OS in patients with pN0-pN1 disease but a statistically significant 6.3% improvement in 5yrOS in patients with pN2 disease. The OS benefit in pN2 disease was dependent on radiation dose with patients receiving 45-54Gy having better outcomes that those treated with doses >54Gy. In patients treated with doses >54Gy, OS was similar to those patients not receiving PORT.[10]

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.[11]

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.[12]

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.[13]

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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. Last reviewed December 2015	I	[7]
Data from three more recent but non-randomised studies suggest a survival benefit for PORT in pN2 disease. Last reviewed December 2015	III-2	[8], [9], [10]

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. Last reviewed December 2015	**C**

Practice point
Post-operative radiation therapy may be considered in the setting of a positive margin. Last reviewed December 2015

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2.17 Mediastinal lymph node dissection

Contents

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[1] , it was found that the evidence already existed for a survival benefit from complete mediastinal lymph node dissection. This was specifically reported in 2006[2], but did not generate the level of interest that accompanies new pharmacological interventions. The randomised trials by Wu et al[3] and Passlick et al[4] 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[5], that it could be inferred that the benefit of complete mediastinal dissection is clearest in stage II and higher NSCLC. A further systematic review and meta analysis by Huang et al[6] included patients with all stages of NSCLC and found no difference in overall survival between complete mediastinal lymph node dissection and systematic lymph node sampling. However this analysis was heavily weighted towards very early pathologic Stage I patients by inclusion of the ACOSOG Z30 trial.[5]

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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. Last reviewed November 2015	I, II	[1], [2], [7], [3], [4], [6]

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 pathologically confirmed (mediastinal node positive) stage IIIA NSCLC. Last reviewed November 2015	**B**

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2.18 Surgery after chemoradiotherapy

Contents

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.[1][2][3] Theoretical improvements in local control with the addition of surgery must be balanced against the increased morbidity and mortality of surgery.

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

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2.18.2.1 Induction chemoradiotherapy and surgery: Randomised controlled trials

Albain et al (RTOG 93-09 / Int 139)[4] 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.

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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. Last reviewed December 2015	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. Last reviewed December 2015	II	[4]

Evidence-based recommendation	Grade
Unselected patients with biopsy confirmed stage IIIA (N2) disease are best treated with chemoradiotherapy alone. Last reviewed December 2015	**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. Last reviewed December 2015

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2.18.4 References

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2.19 Adjuvant chemotherapy

Contents

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.[1] 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.[2] Stage IIIB NSCLC with N3 disease is considered inoperable although surgery may be indicated for carefully selected patients with T4N0-1M0 disease.[3] 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.

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

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.

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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[4] 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.[5][6]

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. Although there was no evidence of difference in the effect of chemotherapy between stage III NSCLC 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.[6]

In the LACE meta-analysis[5], a 17% reduction in risk of death for stage III NSCLC patients was identified with the HR being 0.83 (95% CI, 0.72 - 0.94) in this group. 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 after 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 (≥ 70 years) died from non-lung cancer-related causes, and elderly patients received significantly lower first and total cisplatin doses, and fewer chemotherapy cycles.[7]

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).[8] There is a suggestion that higher exposure to cisplatin (cumulative dose >300mg/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[5] and 1.4% for patients receiving cisplatin-vinorelbine versus 0.4% for those patients receiving cisplatin in combination with other drugs[8].

Interestingly, longer term follow up of IALT[9], which was the largest study in the LACE meta-analysis, showed continued survival 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.[9]

In a more recent randomised controlled trial, Shen et al[10] reported on 140 patients with stage IIIA-pN2 NSCLC who were randomised to receive adjuvant chemotherapy or chemoradiotherapy. However, the study closed early, fell short of its target sample size of 300, and had an inadequate follow-up period. There was no statistically significant difference between treatment groups for overall survival, which was the primary endpoint of the study.[10]

Finally, in a subgroup of NSCLC patients at high risk of significant morbidity, the North American intergroup 0160 /Southwest Oncology Group (SWOG)[11] 9416 reported on 111 patients with T3-T4 N0-N1 superior sulcus tumours. Patients were treated with neoadjuvant 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.[11]

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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. Last reviewed December 2015	I	[6], [5]
The extent of this survival benefit diminishes with time as the number of non-lung cancer deaths accumulates. Last reviewed December 2015	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. Last reviewed December 2015	**A**

Evidence summary	Level	References
Limited evidence from one well-conducted study supports using induction chemoradiotherapy for locoregional control for patients with superior sulcus NSCLC. Last reviewed December 2015	III-3	[11]

Evidence-based recommendation	Grade
Patients with superior sulcus NSCLC may be considered for induction chemoradiotherapy. Last reviewed December 2015	**C**

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.

Last reviewed December 2015

Practice point

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

Figure 1. Neoadjuvant and adjuvant chemotherapy and the MDT

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2.20 Neoadjuvant chemotherapy

Contents

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.

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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

2.20.2.1 Neoadjuvant chemotherapy and surgery versus surgery alone

A recent high-quality, individual patient data-based meta-analysis of 2,385 patients in 15 trials compared chemotherapy and subsequent surgery with surgery alone.[1] The median follow-up period was 6 years for all patients. The patients were mostly men (80%) with a median age of 62 years (IQR 55-68) and good performance status (88%). Patients had predominantly squamous (50%) rather than adenocarcinoma histology (29%). Most patients had clinical stage IB-IIIA NSCLC (93%), and 22.2% patients had stage III disease.

The primary objective of this analysis was overall survival. A clear survival benefit of neoadjuvant chemotherapy was observed (HR 0.87, 95% CI 0.78-0.96; p=0.007). This benefit represented a 13% reduction in the relative risk of death, and translated to a 5% absolute improvement in survival at 5 years from 40% to 45% for all patients. As listed below, the effect of neoadjuvant chemotherapy on survival occurred irrespective of a large number of clinical factors. Consequently, this overall HR of 0.87 was applied to the survival of control group patients, and thus survival at 5 years for stage III patients receiving neoadjuvant chemotherapy improved from 20% to 25%. However, 98% of the stage III patients were stage IIIA, and comprised 21.6% of the total number of patients. Therefore, study results for stage III NSCLC can only be confidently applied to stage IIIA patients.

List of clinical factors that did not influence the effect of neoadjuvant chemotherapy on survival:

(i) age;

(ii) age group (<60, 60-64, 65-69, ≥70);

(iii) histology (adenocarcinoma or squamous);

(iv) performance status (0, 1, 2+);

(v) whether the chemotherapy was given pre-operatively, or both pre-operatively and post-operatively;

(vi) the number of pre-operative chemotherapy cycles (2 or 3);

(vii) the type of chemotherapy regimen (platinum plus second generation chemotherapy, platinum plus third generation chemotherapy, or non-platinum chemotherapy);

(viii) the number of chemotherapy agents (non-platinum single agent regimen [i.e. docetaxel], doublet regimen, or triplet regimen);

(ix) the chemotherapy regimen and the number of chemotherapy agents (non-platinum single agent regimen, platinum second generation [doublet], or platinum second generation [triplet]);

(x) whether the regimen was cisplatin-based or carboplatin-based;

(xi) whether post-operative radiotherapy given or not.

Deferring surgery because of neoadjuvant chemotherapy did not appear to produce an excess of early mortality. This meta-analysis did not identify deleterious effects of neoadjuvant chemotherapy on survival within either 30 days of surgery or 6 months of randomisation (OR 0.88, 95% CI 0.67-1.14, p=0.33; heterogeneity p=0.60). Administering neoadjuvant chemotherapy may have a practical advantage over adjuvant chemotherapy. In 10 of 15 trials in this meta-analysis, the mean compliance rate for neoadjuvant chemotherapy was 85% (range 71-100%),[1] which contrasts with the lower mean compliance rate of 62% (range 41-98%) for adjuvant chemotherapy.[2]

No evidence was found, for or against, to indicate that neoadjuvant chemotherapy improved the likelihood of complete resection by making tumours more operable. Indeed, an effect of neoadjuvant chemotherapy on complete resection rates could not be reliably estimated either because of possible variations in the classification of extent of complete resection or heterogeneity of the effect between trials, especially as the complete resection rate for control patients varied considerably. Furthermore, there was no clear effect of neoadjuvant chemotherapy on time to locoregional recurrence (HR 0.88, 95% CI 0.73–1.07; p=0.20; heterogeneity p=0.89).

As secondary outcomes, neoadjuvant chemotherapy conferred a clear benefit both on recurrence-free survival (HR 0.85, 95% CI 0.76–0.94, p=0.002; heterogeneity p=0.41) and time to distant recurrence (HR 0.69, 95% CI 0.58–0.82; p<0.001; heterogeneity p=0.40). The recurrence-free survival at 5 years improved from 30% to 36%. The time to distant recurrence at 5 years improved from 60% to 70%. This 10% absolute benefit of neoadjuvant chemotherapy on distant recurrence rate at 5 years was greater than the 5% absolute benefit at 5 years for adjuvant chemotherapy, and suggests that neoadjuvant chemotherapy may have greater potential to eradicate micrometastases. Moreover, there was a difference in effect by chemotherapy scheduling (p=0.05) for time to distant recurrence. A substantially greater relative benefit existed for those responding patients who also received adjuvant chemotherapy (HR 0.53, 95% CI 0.39–0.73, p<0.001) than for those who received neoadjuvant chemotherapy alone (HR 0.78, 95% CI 0.63–0.96, p=0.02).

The value of adding neoadjuvant radiotherapy to neoadjuvant chemotherapy and surgery was investigated recently using a randomised trial design. In a study of 232 patients with pathologically proven stage IIIA/N2 NSCLC, Pless et al (2015) allocated 117 patients to receive chemoradiotherapy and 115 patients to receive chemotherapy.[3] The primary endpoint was event-free survival. There was no significant difference in the median event-free survival between the two groups, and median overall survival also did not differ significantly. Hence, radiotherapy did not add any benefit to induction chemotherapy followed by surgery. The authors suggested that one definitive local treatment modality combined with neoadjuvant chemotherapy is adequate to treat resectable stage IIIA/N2 NSCLC.

In a recent systematic review and meta-analysis, Xu et al (2015) aimed to determine (i) the survival benefit of multimodality therapy including surgery to stage IIIA/N2 NSCLC patients and (ii) if neoadjuvant chemoradiotherapy was superior to neoadjuvant chemotherapy in stage IIIA/N2 NSCLC patients.[4] Seven trials involving 1049 patients were included in this study. There was no significant difference in OS or PFS in stage IIIA /N2 NSCLC patients who received neoadjuvant chemotherapy or chemoradiotherapy before surgery compared to those who received neoadjuvant chemotherapy or chemoradiotherapy before radical radiotherapy. These data lend further support to the notion that one definitive local treatment modality combined with neoadjuvant chemotherapy is adequate to treat resectable stage IIIA/N2 NSCLC.

Until the recent report of the NSCLC Meta-analysis Collaborative Group, which was based on individual patient data, reliable evidence had not been available to show a consistently beneficial survival effect of neoadjuvant chemotherapy in stage III NSCLC.[1]

The earlier systematic review and literature-based meta-analysis had been based on a relatively small number of trials and patients: seven randomised controlled trials and 988 patients. Neoadjuvant chemotherapy was found to increase survival with a HR of 0.82 (95% CI, 0.69 - 0.97; p=0.022). There was no evidence of statistical heterogeneity, and when this HR was applied across all stages of disease, it gave an equivalent absolute survival benefit of 6%, increasing overall survival from 14% to 20% at 5 years. However, this analysis had been unable to establish if stage III NSCLC patients benefit more or less from neoadjuvant chemotherapy.[5] An indirect comparison meta-analysis had been performed to obtain the relative hazards on survival of postoperative to preoperative chemotherapy administration in patients with resectable NSCLC.[6] 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.[6] 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.[7] The quality of evidence in this study was low with a substantial risk of bias.

Finally, other recent but low-quality and biased studies do not weigh against the strength of evidence provided by the NSCLC Meta-analysis Collaborative Group.[1]

Katakami et al (2012)[8] performed a randomised controlled trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy in 60 patients with stage IIIA-pN2 NSCLC by. This study was too small because slow accrual had led to early closure. No statistically significant difference between treatment arms was found. Chen et al (2013)[9] reported on a study of 356 NSCLC patients (including 122 patients with stage IIIA disease) who were randomised to surgery alone or neoadjuvant chemotherapy then surgery. No effect of neoadjuvant chemotherapy was detected in patients with stage IIIA disease. Unfortunately, critical data were missing in this

study, preventing a reliable assessment of outcomes to be made. Horita et al (2013)[10] performed a meta-analysis of aggregated patient data from 16 randomised controlled trials of a total of 2,385 patients, which included 1,447 stage IIIA patients. A meta-analysis was also performed for the seven studies that evaluated only patients with stage III NSCLC. For 1,447 patients and 1,068 deaths, the pooled HR for OS was 0.77 (95% CI, 0.68-0.87; $p < 0.001$). In this group of stage III disease studies, the heterogeneity was low and was not significant ($I^2 = 17\%$; p for $x^2 = 0.300$ [<0.01]). However, the heterogeneity between the pooled HR for studies only with stage III patients and those without stage limitation was high and significant ($I^2 = 69\%$; p for $x^2 = 0.073$ [<0.01]). In addition, in the remaining group of nine studies without stage limitation, moderate heterogeneity was found, and was significant ($I^2 = 47\%$; p for $x^2 = 0.059$ [<0.01]). Furthermore, in this meta-analysis evaluating only patients with stage III NSCLC, three of the seven studies contributed the majority both of patients (1,217) and deaths (903), but these studies were of poor quality using the Chalmers score.

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2.20.2.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients with clinical stage IIIA disease treated by surgery, neoadjuvant chemotherapy reduces the relative risk of death by 13%, and improves absolute 5 year survival rates from 20 to 25%. Last reviewed December 2015	I	[1]

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**A**

Practice point
Patients whose tumours respond to preoperative chemotherapy may derive additional survival benefit from postoperative chemotherapy. Last reviewed December 2015

Practice point

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

Neoadjuvant and adjuvant chemotherapy and the MDT

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2.20.3 References

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2.21 Neoadjuvant radiotherapy plus neoajuvant chemotherapy

Contents

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[1][2][3] based on the very poor survival of patients treated with surgery alone in this setting.[4][5][6][7] 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.

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

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2.21.2.1 Randomised controlled trials of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy

Girard et al (IFCT – 0101)[8] 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[9][10] and a third well designed trial attempted by the RTOG and abandoned due to poor accrual[11] only one phase 3 study (enrolling a majority of cIIIB patients) has ever been published.

Thomas et al[12][13] 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.

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2.21.3 Evidence summary and recommendations

Evidence summary	Level	References
Neoadjuvant chemotherapy, with or without radiotherapy, is feasible. Last reviewed December 2015	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. Last reviewed December 2015	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. Last reviewed December 2015	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. Last reviewed December 2015	**C**

Practice point

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

Last reviewed December 2015

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2.21.4 References

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2.22 Recommended treatment approach

Contents

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.[1]

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.

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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

2.22.2.1 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.[2] 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.

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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.[3] 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%.[4]

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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.[5][6][7][8][9][10][11]

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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.[12] A variety of chemotherapy regimens were used. Eleven trials used cisplatin-containing regimens while the remaining trials used alkylating agents such as cyclphosphamide 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 ration 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 carbopatin-based chemotherapy.[13] 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.[14] 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.[9][10][11].

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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.[15] The concurrent administration of chemoradiotherpay 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%CI0.62-0.89), representing a 10% survival benefit at two years.[14]

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 ≥ 5% were excluded and elderly patients were poorly represented.

2.22.2.3.3 Elderly patients

A phase 3 trial by the Japan Clinical Oncology Group, randomised 200 patients with unresectable Stage III disease, ECOG performance status 0-2 and a median age of 77 years (range 71-93 years) to chemoradiotherapy (using low-dose carboplatin) or radiotherapy alone. Chemoradiotherapy was associated with a statistically significant improvement in median OS (22.4m v 16.9m, HR 0.68, 95%CI 0.47-0.98, p=0.0179), and a higher incidence of grade 3-4 haematological side effects but not difference in pulmonary toxicity.[16]

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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. Last reviewed December 2015	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 survival benefit compared with radiation therapy alone Last reviewed December 2015	I	[13], [12], [14]
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. Last reviewed December 2015	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. Last reviewed December 2015	**A**

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.

Last reviewed December 2015

Practice point

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.

Last reviewed December 2015

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2.22.4 References

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2.23 Optimal radiation dose and fractionation schedule

Contents

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.[1] Attempts to improve loco-regional control and survival include radiation dose escalation using either conventional or altered fractionation schedules.

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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).[2] 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.[3] 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 rage of 63-103Gy.[4] 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.[5]

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

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

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.[12] 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.[13] The final analysis found that 74Gy given in 2Gy fractions with concurrent chemotherapy was not better than 60Gy plus concurrent chemotherapy for patients with Stage III NSCLC and might be potentially harmful.[14] The addition of cetuximab to concurrent chemoradiation and consolidation treatment provided no benefit in overall survival. There was a clinically significant meaningful decline in QOL in the 74Gy at 3 months. [15]

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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.[10] The loss of survival rate was 1.6% per day of prolongation beyond six weeks. [16] 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 hyperfractioned 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.[17] [18] 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) randomsed 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.[19]

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)[20] 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.[21]

The North Central Cancer Treatment Group (NCCTG) randomised 110 patients with PS ≤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.[22]

A second NCCTG trial randomised 246 patients with stage III NSCLC and ECOG PS ≤ 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).[23] 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).[24] This hyperfractionated RT regimen was derived from a preceding RTOG dose escalation study.[25] 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).[26] 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.

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2.23.3 Evidence summary and recommendations

Evidence summary	Level	References
A radiation dose- response relationship exists for NSCLC Last reviewed December 2015	II	[2]
Radiation dose is a prognostic factor for OS in NSCLC	III-2	[4]

Evidence summary	Level	References
Last reviewed December 2015		
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). Last reviewed December 2015	II	[2]
A radiation dose of 74Gy used in the definitive management of stage III disease (with concurrent chemotherapy) is not better than 60Gy and may be potentially harmful. Last reviewed December 2015	II	[14]

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**B**

Evidence summary	Level	References
Prolongation of overall treatment time is detrimental to tumour control and survival in NSCLC. Last reviewed December 2015	III-2	[10]
CHART is associated with a survival advantage compared with conventional radiotherapy alone. This survival advantage was most pronounced in patients with squamous cell histology. Last reviewed December 2015	II	[17], [18]
Accelerated radiotherapy given with chemotherapy, either sequentially or concurrently is not associated with a survival advantage over conventional radiotherapy given with chemotherapy, either sequentially or concurrently. Last reviewed December 2015	II	[21], [20]

Evidence summary	Level	References
Hyperfractionated radiotherapy given either alone or with chemotherapy is not associated with a survival advantage over conventional radiotherapy given either sequentially or concurrently with chemotherapy. Last reviewed December 2015	II	[22], [26], [24], [23]

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. Last reviewed December 2015	**B**

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2.23.4 References

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2.24 Principles of radiation therapy

Contents

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

The principles of radiation therapy used in the definitive management of Stage III inoperable NSCLC can be found in the eviQ guidelines.

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.

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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.[1] 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).[2] The use of CT-based treatment planning is associated with a survival advantage in a non-randomised population based study.[3]

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

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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.[5][6][7] Thus, the application of “standard margins” around tumours to account for mobility can lead to geographic miss and unnecessary normal tissue irradiation.[8][9] The use of planning methods to evaluate and account for tumour motion is recommended.[10]

Acceptable methods, according to the AAPM Task Group 76 guideline,[10] 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

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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.[11] The measured diameter of tumours in lung parenchyma and mediastinum is dependent on the window width and level chosen to analyse CT slices.[12] The appropriate window settings should be used when contouring the parenchymal and nodal disease. Lymph nodes with a short axis diameter ≥ 1cm 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.[13][14]

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.[15] FDG-PET scans enable more accurate differentiation of viable tumour tissue from surrounding consolidated lung,[15] are superior to CT scans in demonstrating mediastinal node involvement[16] and reduce inter-observer variability in delineating target volumes.[17] However, there is no data demonstrating an improvement in survival or local recurrence with the incorporation of PET data into CT-based planning.[18] 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.[19]

The Clinical Target Volume (CTV) encompasses the GTV plus an antomically defined area thought to harbour micrometastases.[11] Giroud et al performed a quantitative assessment of microscopic extension on histological slides from “well insufflated” resected NSCLC cases.[20] 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.[21] 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.[22] 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%).[23]

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).[24][23] 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)[11]

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.

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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 ≤ 30 -35% and the Mean total lung dose (MLD) be limited to ≤ 20-23Gy (with conventional fractionation) to limit the risk of radiation pneumonitis to ≤ 20% in definitely treated patients with NSCLC.[25]

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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.[26] 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.[27]

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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 Vdose parameters correlated significantly with severe acute oesophagitis.[28] 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.[29] The ongoing Phase III Intergroup trial (RTOG 0617) has recommended (but not mandated) that the mean dose to the oesophagus be kept to <34Gy.[30] 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.[31]

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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:[32] 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.[30]

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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.[33]

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

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.[34]

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2.24.3 Evidence summary and recommendations

Evidence summary	Level	References
The use of an immobilisation device for patient simulation minimises set-up errors. Last reviewed December 2015	III-2	[1]

Evidence-based recommendation	Grade
Patients can be simulated in the treatment position using an immobilisation device.	**C**

Evidence-based recommendation	Grade
Last reviewed December 2015	

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. The use of CT-based treatment planning is associated with a survival advantage in a non-randomised population based study. Last reviewed December 2015	III-2	[33], [3]

Evidence-based recommendation	Grade
Treatment planning utilising multi-slice CT image acquisition and a 3D planning system is encouraged. Last reviewed December 2015	**C**

Practice point
Treatment planning may utilise an accepted method of evaluating and accounting for tumour motion. Last reviewed December 2015

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. Last reviewed December 2015	III-2	[12]

Evidence-based recommendation	Grade
The appropriate window settings may be used when contouring the parenchymal and nodal disease. Last reviewed December 2015	**C**

Practice point
Individual characteristics of breathing and variations associated with tumour location and pulmonary and tumour pathology lead to individual patterns of tumour motion. Last reviewed December 2015

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 Last reviewed December 2015	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. Last reviewed December 2015	**B**

Evidence summary	Level	References
Intravenous contrast may assist in target delineation especially in centrally located tumours or tumours associated with nodal disease. Last reviewed December 2015	III-2	[4]

Evidence-based recommendation	Grade
Tumour volume delineation may be assisted by the use of intravenous contrast during simulation. Last reviewed December 2015	**C**

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. Last reviewed December 2015	III-2	[20]

Evidence-based recommendation	Grade
The Clinical Target Volume may encompass the Gross Tumour Volume plus a margin of 6-8mm. Last reviewed December 2015	**C**

Practice point
-The Gross Tumour Volume may encompass the visible disease (both primary and nodal) on CT and/or CT-PET.

Practice point
-The Clinical Target Volume may encompass the Gross Tumour Volume plus a margin to account for microscopic extension of disease . -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). Last reviewed December 2015

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%) Last reviewed December 2015	II, IV	[23], [21], [24], [22]

Evidence-based recommendation	Grade
Elective nodal irradiation is not recommended. Last reviewed December 2015	**C**

Practice point
Normal Tissue Dose Volume Constraints 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. Lung: V20 ≤ 30 -35% , Mean total lung dose (MLD) ≤ 20-23Gy A total dose of 50Gy in 2Gy/f to the full spinal cord cross-section is associated with a 0.2% risk of myelopathy.

Practice point

Spinal Cord: 50Gy in 1.8-2.0Gy/f

Last reviewed December 2015

Practice point

A single best threshold volumetric parameter for oesophageal irradiation has not been identified.

Last reviewed December 2015

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2.25 Concurrent chemoradiotherapy best practice

Contents

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 and who do not have a mutation for targeted therapy?

2.25.1.1 Introduction

Patients with inoperable NSCLC can be divided into three groups:[1]

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 ≥60Gy
2. Patients with poor PS, substantial weight loss (>10%) and advanced disease for whom simple palliative measures are appropriate; and
3. An intermediate group of patients who have a good PS but locally advanced disease for whom radical chemo-radiation (≥60Gy) is not feasible either due to tumour extent or patient factors (such as poor respiratory function).

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

Recommendations in this section apply to patients in groups 2 and 3 who do not have a mutation for targeted therapy. In either group the aim of treatment is to palliate symptoms and maintain quality of life.

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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.[2][3] The authors concluded that there was strong evidence, from four studies[4][5][6][7] for an increase in survival in patients with good PS who were given higher dose RT. One large high-quality RCT showed an increase in survival of 5% at one year and 3% at two years.[4] A formal meta-analysis was not attempted due to the apparent heterogeneity of the studies.

An update of this Cochrane review attempted a sub-group analysis by PS. The use of more fractionated palliative regimens to prolong survival in patients with good PS was not supported by strong evidence.[3] The authors warn that as data was only available for 56% of patients and there was significant heterogeneity, this conclusion needed to be treated with caution.

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.[8] 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 ($\geq 35Gy_{10}$ 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.

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.[9]

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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≤ 0.0001), resulting in an absolute improvement in one year survival of 9% (from 20% to 29%).[10] Studies which prospectively evaluate intrathoracic tumour-related symptoms demonstrate an improvement from baseline scores with palliative chemotherapy.[11]

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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.

A trial conducted by the Norwegian Lung Cancer Study Group compared the use of palliative concurrent chemoradiation (three weekly carboplatin + oral vinorelbin + 42Gy/15f commencing with the second cycle) with the same chemotherapy alone in the management of patients with locally advanced, inoperable NSCLC not suitable for curative radiotherapy.[12] The trial was closed due to slow accrual with the recruitment of 191 patients. However, the use of chemoradiation was associated with a statistically significant improvement in median overall survival (12.6m versus 9.7m, p<0.01) and in health related quality of life, but with more hospital admissions related to side effects.

2.25.3 Evidence summary and recommendations

Evidence summary	Level	References
Palliative radiotherapy achieves reasonable rates of symptom control. Last reviewed December 2015	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. Last reviewed December 2015	**A**

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. Last reviewed December 2015	I	[8]

Evidence-based recommendation	Grade
The patient’s performance status should be taken into consideration when choosing the radiation dose and fractionation pattern:	**A**

Evidence-based recommendation	Grade
- 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. - Patients with poor performance status should be treated with short courses of treatment. Commonly employed radiotherapy regimens include 10Gy/1f, 16Gy/2f (1f/week). Last reviewed December 2015	

Evidence summary	Level	References
As in metastatic disease, in locally advanced Stage III NSCLC, systemic chemotherapy improves survival and maintains QOL compared with best supportive care. Last reviewed December 2015	I	[10]

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 systemic therapy is recommended. Last reviewed December 2015	**A**

Evidence summary	Level	References
For patients with locally advanced, inoperable Stage III NSCLC who are not fit for curative radiotherapy, the use of concurrent palliative chemoradiation is superior to chemotherapy alone with respect to survival and HRQOL but is associated with more side effects necessitating admission to hospital. Last reviewed December 2015	II	[12]

Evidence-based recommendation	Grade
For patients with locally advanced, inoperable Stage III NSCLC not fit for curative therapy, consideration should be given to concurrent administration of palliative chemoradiation. Last reviewed December 2015	**B**

Practice point
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

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2.25.4 References

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2.26 Pancoast tumours

Contents

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.[1]

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.

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

The presence of Pancoast syndrome is not a prerequisite for a tumour to be defined as a Pancoast tumour.[1] 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.

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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.[2]

Absolute and relative contra-indications to surgery based on preoperative imaging findings have been suggested.[3] 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.

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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%.[4] 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.[5] 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[6] but longterm survival remained poor with five-year survival figures of 5 -23%.[7] A review of 23 studies employing bimodality therapy of radiation followed by surgical resection demonstrated a mean five-year survival of 36.5%.[7] Local relapse was reported in 40% of patients undergoing bimodality therapy.[8] 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.[9] More intensive preoperative regimens using doses approaching 60Gy[10] [11] or hyperfractionated accelerated radiation therapy[12] 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/m2 followed by surgical resection has been employed in the Netherlands[13][14]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.[15] 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.

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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?)[16]

A regimen of accelerated radiotherapy (66Gy in 24 fractions, 2.75Gy/f given over 32 days, using concomitant boost) and concurrent daily cisplatin 6mg/m2 has been employed in the Netherlands.[13][14] 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.[6]

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2.26.3 Evidence summary and recommendations

Evidence summary	Level	References
No Phase III study has addressed the optimal management of Pancoast tumour Last reviewed December 2015		
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. Last reviewed December 2015	III-3, IV	[5], [4]
The optimal regimen for preoperative chemoradiotherapy has not been established. Last reviewed December 2015		
No studies have determined whether preoperative chemoradiation therapy is superior to surgical resection followed by postoperative chemoradiation. Last reviewed December 2015		

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. Last reviewed December 2015	**C**

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. Last reviewed December 2015	I	[16]

Evidence-based recommendation	Grade
For patients with unresectable Pancoast tumours and good performance status, the concurrent administration of chemotherapy and radiotherapy is recommended. Last reviewed December 2015	**A**

Evidence summary	Level	References
Radiation therapy alone can be used to palliate symptoms in patients with unresectable Pancoast tumours and poor performance status or distant metastases. Last reviewed December 2015	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. Last reviewed December 2015	**C**

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

Contents

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. 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).[1] 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.[2] 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.[3] 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%.

Sahgal et al conducted a meta-analysis of three randomised trials evaluating SRS with or without adjuvant WBRT.[4] Distant brain failures were reduced from 53% to 34% with adjuvant WBRT, and neurological deaths from 30% to 25%. Median survival was similar being 10 months with SRS alone and 8.2 months with SRS and WBRT.

A Cochrane systematic review of the same three trials included in the Sahgal et al meta-analysis concluded that the addition of WBRT following SRS significantly improved local brain metastasis control and distant brain control without any statistically difference in overall survival.[5]

WBRT has an impact on patients' quality of life. The EORTC randomised trial is the only trial which has measured this prospectively. Patients receiving WBRT had worse Health Related Quality of Life scores than the observation group.[6] This was significant for physical functioning and fatigue at 8 weeks, global health status at 9 months, and cognitive functioning at 12 months after treatment.

The commonest dose for adjuvant WBRT was 30Gy in 10 fractions.[3][2] This dose was associated with mild acute toxicity (13% brisk skin erythema or dry desquamation, 10% moderate to severe nausea or vomiting, 4% severe headache).[3] Late Grade 3 effects occurred in 2-22% and Grade 4 1-4% with no difference between the observation and WBRT arms in the EORTC study.[3] The WBRT dose was higher in the Patchell study (50.4Gy in 28 fractions) and toxicity was not reported.

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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. Last reviewed September 2015	I, II	[3], [4], [5]
Adjuvant whole brain radiotherapy following surgical resection or radiosurgery for one to three brain metastases does not improve survival or patient functional status. Last reviewed September 2015	I, II	[3], [4], [5]
Adjuvant whole brain radiotherapy following surgical resection or radiosurgery for one to three brain metastases is associated with a reduction in health related quality of life. Last reviewed September 2015	II	[6]

Evidence-based recommendation	Grade
Routine adjuvant whole brain radiotherapy is not recommended following surgical resection or radiosurgery for brain metastases. Last reviewed September 2015	**A**

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2.27.3 References

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2.28 Resection of brain metastasis

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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.[1] 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. [2]

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. [1]

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 [1] and around 40% of these are due to NSCLC [2], 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 determined 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[3]) but also to guide choice of systemic chemotherapy or targeted therapy.

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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. [3][4][5][6] 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[3]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 [4][5] 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 [6] 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.

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

A meta analysis by Hart et al [1] 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 (I2 = 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.

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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. Last reviewed December 2015	I, II	[1], [3], [4], [5]
Improvement in long-term survival in unselected patients based on the addition of surgery to WBRT is unlikely. Last reviewed December 2015	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]

Evidence summary	Level	References
Last reviewed December 2015		
Addition of surgery to WBRT may reduce the proportion of deaths due to neurological cause and may improve Functionally Independent Survival Last reviewed December 2015	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. Last reviewed December 2015	**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. Last reviewed December 2015	**C**

Practice point
Surgery may control symptoms more quickly than WBRT and is reasonable in cases of impending neurological emergency. Last reviewed December 2015

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. Last reviewed December 2015

Practice point

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

Last reviewed December 2015

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.

Last reviewed December 2015

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2.29 Resection of primary disease after complete resection of metastatic disease

Contents

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.

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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.

A recent systemic review of publications reporting patients with isolated metastasis to sites other than brain or adrenal accumulated 62 patients undergoing complete resection of metastatic site after definitive treatment of primary. The study found a clinically and statistically significant difference on multivariate analysis in survival with a hazard ratio of 8.2 (95%CI:2.1–32.5),p=0.003, for involvement of mediastinal lymph nodes. [1]

The only published prospective phase II study was reported by Downey et al[2] 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.

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2.29.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients with isolated metastasis to sites other than brain or adrenal and mediastinal nodal involvement complete resection of metastatic site after definitive treatment of primary does not result in cure. Last reviewed December 2015	IV	[1]

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.

Last reviewed December 2015

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.

Last reviewed December 2015

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2.30 Radiotherapy

Contents

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.[1] 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.

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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

Stevens et al conducted a systematic review of 14 randomised controlled trials which randomised between different doses of palliative radiotherapy.[2] 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 higher radiation doses (20Gy in 5 fractions - 50Gy in 25 fractions). The meta-analysis showed a statistically significant improvement in one year survival with fractionated regimens in patients with good performance status (RR=0.95, CI: 0.90-0.99) but not in those with poor performance status (RR=0.96, CI 0.91-1.02).

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%.[3][4][5][6] The median duration of palliative benefit for cough is 56-78 days, chest pain 56-74 days and haemoptysis 64-146 days.[3][4] 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.[2] A higher radiotherapy dose (30Gy in 10 fractions) has been associated with a longer duration of response and a slower progression of symptoms.[7] There is greater improvement in quality of life with higher radiotherapy doses (20Gy in 5 fractions).[8] Higher doses (20Gy in 5 fractions, 30-39Gy in 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.[2][5][8][7] 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.

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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.[2] Higher radiotherapy doses have been associated with increased toxicity particularly oesophagitis which can occur in 40-56% of patients.[3][4] More recent trials have shown no difference in acute toxicity between lower and higher doses of radiotherapy.[8][7] 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.[3][4][5] This can be reduced by limiting the spinal cord dose to LQED2 of 48Gy.[9]

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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.[10] 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.

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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.

Reveiz systematically reviewed 14 randomised controlled trials comparing endobronchial brachytherapy to external beam radiotherapy and other interventions such as chemotherapy and laser.[11] 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.

There has been one randomised trial evaluating the dose of endobronchial brachytherapy.[12] 142 patients with centrally located malignant tumours were randomised between 4 fractions of 3.8Gy and 2 fractions of 7.2Gy. Local tumour response as assessed at bronchoscopy was significantly greater for the 2 fraction course. There was no significant difference in fatal haemoptysis or survival.

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2.30.2 Evidence summary and recommendations

Evidence summary	Level	References
Palliative thoracic radiotherapy can relieve symptoms due to primary lung cancer. Last reviewed December 2015	I	[2]
Lower doses of radiotherapy (10Gy in 1 fraction, 17Gy in 2 fractions) are equivalent to higher doses (20Gy in 5 fractions, 30-39Gy in 10-13 fractions and higher) in terms of symptom palliation. Last reviewed December 2015	I	[2]
In patients with good performance status, higher doses of radiotherapy (20Gy in 5 fractions, 30-39Gy in 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. Last reviewed December 2015	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. Last reviewed December 2015	I	[2]
Patients with minimal thoracic symptoms do not benefit from immediate thoracic radiotherapy. Last reviewed December 2015	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. Last reviewed December 2015	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. Last reviewed December 2015	**A**

Evidence-based recommendation	Grade
Patients who are of poor performance status should be treated with lower doses of palliative thoracic radiotherapy (8-10Gy in 1 fraction, 16-17Gy in 2 fractions) as this provides equivalent symptomatic response to higher doses of radiotherapy (20Gy in 5 fractions, 30-39Gy in 10-13 fractions). Last reviewed December 2015	**A**

Evidence-based recommendation	Grade
Patients who are of good performance status should be treated with higher doses (20Gy in 5 fractions, 30-39Gy in 10-13 fractions) of palliative thoracic radiotherapy in order to maximise duration of palliation and survival. Last reviewed December 2015	**B**

Practice point
Patients with a centrally located lung cancer who are at risk of major airway obstruction should be considered for palliative thoracic radiotherapy, even in the absence of symptoms. Last reviewed December 2015

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2.31 Radiotherapy to the brain for patients with inoperable brain metastases

Contents

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.[1] Brain relapse is higher in stage III NSCLC ranging from 27%-55% after curative treatment.[2][3][4] 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.

There are two prognostic models which may help guide treatment in patients with brain metastases.The RTOG has divided patients with brain metastases, from all primary sites, into three prognostic groups based on recursive partitioning analysis (RPA).[5]

- RPA Class I – Age <65, Karnofsky performance index ≥=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.

Sperduto et al have devised a model specific to NSCLC which includes the variables of age, Karnofsky performance status (KPS), extra-cranial disease and the number of brain metastases.[6] See *Figure 1. Non-small-cell and small-cell lung cancer Graded Prognostic Assessment (GPA) worksheet* below.

These prognostic models should be used to help guide treatment recommendations.

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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

There is only one randomised study which has compared WBRT plus best supportive care including steroids (BSC) compared to BSC alone for patients with brain metastases from NSCLC in whom the attending clinician was uncertain of the value of WBRT.[7] An interim analysis after randomisation of 151 patients, has shown no significant difference in survival (49 days in the WBRT group vs 51 days in the BSC BSC group) or quality of life. The final results of this trial have been presented in abstract form.[8] The study population of 538 patients was representative of the clinic population with a median age of 66 years, poor performance status (KPS<70) in 38% and the presence of extracranial metastases in 54%. There was no significant difference in median survival (65 days WBRT vs 57 days BSC), quality of life or steroid use between the groups.

Pease et al also conducted a systematic review which included non-randomised trials.[9] The median survival of patients undergoing radiotherapy was 3.2-5.8 months. Historical data shows a median survival of 2-3 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.

Tsao et al conducted a systematic review of 39 randomised controlled trials of whole brain radiotherapy in 10835 participants.[10] These trials included patients with brain metastases from different primary cancers, although in the majority of trials over half the participants had lung cancer. Compared to 30Gy in 10 fractions, higher doses and longer fractionation schemes resulted in similar survival, symptom control and improvement in neurological function.

There have been many randomised trials of different radiotherapy dose and fractionation schemes for whole brain radiotherapy.[11][12][13][14][15][16] 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.[11] 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.[17][13][14][15][16] 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.[13][14][16] 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).[15]

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%.[11][15][13] 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.[11]

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2.31.1.2.2 Toxicity

Toxicity was poorly reported in most trials. Many patients develop temporary alopecia.[15] 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.[16]

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2.31.2 Evidence summary and recommendations

Evidence summary	Level	References
Whole brain radiotherapy can palliate symptoms from brain metastases. Last reviewed December 2015	I	[10]
Radiotherapy doses of 20Gy in 5 fractions or 30Gy in 10 fractions are equivalent to higher doses in terms of survival, palliation of symptoms and neurological function. Last reviewed December 2015	I, II	[11], [10]
In patients with multiple brain metastases who are of good performance status, whole brain radiotherapy may improve survival compared with best supportive care. Last reviewed December 2015	III-3	[9]

Evidence summary	Level	References
Patient age, performance status, status of extra-cranial disease and number of brain metastases are strong prognostic factors for survival. Last reviewed December 2015	II, IV	[5], [6]
In patients with adverse prognostic factors for whom the clinician is uncertain of the value of whole brain radiotherapy, the use of best supportive care and steroids results in similar overall survival and quality adjusted survival compared with whole brain radiotherapy. Last reviewed December 2015	II	[7]

Evidence-based 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. Last reviewed December 2015	**A**

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 improvement in neurological function. Last reviewed December 2015	**B**

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**B**

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2.32 Stereotactic radiosurgery in the treatment of brain metastases

Contents

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.

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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,[1] 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, on univariate analysis. However, on multivariate analysis SRS boost was not significantly associated with an improvement in survival. SRS boost was associated with significantly improved local control in the brain at 12 months (82% vs 71%). There was no difference in neurological deaths. These findings are supported by a small randomised trial reported by Kondziolka et al.[2]

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).

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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.[3] They could not show any advantage of one treatment over the other due to lack of randomised evidence. Qin et al conducted a systematic review of patients with solitary brain metastasis from NSCLC.[4] All study types were included resulting in 2 clinical control studies and 16 retrospective case series. Median survival was similar for those having neurosurgery (12.7 months) and SRT (14.9 months) as were 1, 2 and 5 year survival.

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.[5] 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. There are single institution retrospective cohort studies which have compared surgery to SRS.[6][7][8][9][10] 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,[6][7][8][9] and three showed better local control with SRS.[7][8][9]

Auchter et al performed a retrospective multicentre study on patients with a solitary metastasis who would have met the eligibility criteria for Patchell trial of surgical resection.[11][12] 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.[12][13][14]

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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. Last reviewed December 2015	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. Last reviewed December 2015	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. Last reviewed December 2015	III-2	[7], [8], [6]

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. Last reviewed December 2015	**C**

Practice point
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

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. Last reviewed December 2015	C

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2.32.3 Issues requiring more clinical research study

- What is the role of stereotactic radiosurgery following surgical resection of brain metastases?

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2.32.4 References

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2.33 Radiotherapy to the bone metastatic disease

Contents

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.[1] Other potential complications include pathologic fracture, nerve root compression or spinal cord compression.

The risk of pathological fracture should be assessed before prescribing palliative radiotherapy. The Mirel score[2] has been suggested as a risk assessment tool, with high sensitivity but low specificity.[3] Mirel's recommendations are to proceed with radiotherapy for scores ≤7 and to refer for prophylactic fixation for scores ≥9. Clinical judgement should be used for a score of 8. Patient factors such as performance status, metastatic tumour burden, suitability for systemic therapies and fitness for anaesthetic should also be taken into account. See *Table 1. Scoring System* from Mirels et al 1989.

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2.33.1.2 Radiotherapy dose and fractionation for palliative radiotherapy to bony metastases

2.33.1.2.1 Cost-effectiveness of radiotherapy

Cost-effectiveness studies of randomised controlled trials from the Netherlands,[4][5] USA[6] and Australia[7] also show a cost saving for single fraction radiotherapy, even when accounting for the higher rate of retreatment. Konski et al[6] 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.[7]

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2.33.1.2.2 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.[8][9][10]

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).[8][9][10] 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.[10]

The most recent meta-analysis of 5000 patients showed an overall response rate of 58% with single fraction and 59% with fractionated radiotherapy.[8] 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.[4] 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 fracionated radiotherapy and complete response rates were 14% in each arm.[4][11] 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.

There has been one randomised trial which compared 8Gy in 1 fraction to 4Gy in 1 fraction.[12] Lung cancer patients comprised 35% of the study population. The actuarial response rate at 4 weeks was significantly better for the 8Gy than the 4Gy arm, 80% vs 68% respectively.This difference remained significant up to a year after treatment. Twice as many patients in the 4Gy arm needed retreatment.

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.[13] There was no difference in the incidence of spinal cord or cauda equina compression.

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2.33.1.2.3 Toxicity

There is no difference in acute toxicity or quality of life between single fraction and fractionated radiotherapy treatment for painful bony metastases.[8][10][4]

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2.33.1.2.4 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[14] 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).[15]

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2.33.2 Evidence summary and recommendations

Evidence summary	Level	References
Palliative radiotherapy can relieve pain from bony metastases. Last reviewed December 2015	I	[8], [9], [10]
A single 8Gy fraction is superior to a single 4Gy fraction of radiotherapy in providing pain relief. Last reviewed December 2015	II	[12]
A single 8Gy fraction of radiotherapy provides equivalent pain relief to a fractionated course of radiotherapy to higher doses. Last reviewed December 2015	I	[8], [9], [10]
A single 8Gy fraction of radiotherapy is associated with higher rates of radiotherapy retreatment. Last reviewed December 2015	I	[8], [9], [10]
A single 8Gy fraction of radiotherapy is associated with higher rates of pathological fracture, although the absolute difference is less than 1-2%. Last reviewed December 2015	I, II	[8], [4]
There is no difference in toxicity and quality of life between single fraction radiotherapy and a fractionated course Last reviewed December 2015	I, II	[8], [4]
Adjuvant radiotherapy after fixation of a pathological fracture can improve functional status. Last reviewed December 2015	III-3	[14]

Evidence-based recommendation	Grade
Patients who have pain from bony metastases (not at risk of pathological fracture) should be offered palliative radiotherapy. Last reviewed December 2015	**A**

Evidence-based recommendation	Grade
A single fraction of 8Gy is recommended if the clinical endpoint is pain relief. Last reviewed December 2015	**A**

Evidence-based recommendation	Grade
Patients who have had orthopaedic fixation of a pathological fracture may be considered for adjuvant radiotherapy. Last reviewed December 2015	**C**

Practice point
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

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2.33.3 References

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2.34 Radiotherapy in metastatic spinal cord compression

Contents

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.

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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)[1] 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.

Chen et al conducted a meta-analysis of studies which evaluated surgery (with or without adjuvant radiotherapy) or radiotherapy for metastatic spinal cord compression.[2] All study types were included but there were no randomised controlled trials found. Patients undergoing surgery had significantly improved ambulation (22% vs 12%), better pain relief (89% vs 69%) and better one year survival than those undergoing radiotherapy alone. However results were not reported by primary tumour site, single versus multi-level spinal cord compression or whether or not systemic therapies were used, all of which can impact on functional outcomes and survival.

Surgery is of benefit to those patients who have unstable spines as a result of their cancer. The SINS score has been found to have good inter- and intra-observer reliability for assessing spinal stability.[3] See *Table 1. SINS* from Fourney et al 2011. A score of 0-6 denotes stability, 7-12 indeterminate stability and 13-18 instability. A surgical consultation is recommended for patients with SINS scores ≥7. Patient factors such as performance status, metastatic tumour burden, suitability for systemic therapies and fitness for anaesthetic should also be taken into account.

For patients treated with radiotherapy alone, there have been two randomised trials of different dose fractionation regimens.[4][5] Maranzano et al randomised 300 patients with an expected life expectancy greater than six months and no indication for surgery to 16Gy in 2 fractions or a split course of 15Gy in 3 fractions

followed by 15Gy in 5 fractions.[4] Two hundred and seventy-six patients were available for analysis and 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. Rades et al randomised 203 patients with no indication for surgery to 20Gy in 5 fractions or 30Gy in 10 fractions.[5] One hundred and fifty-five patients were available for analysis and 37% had lung cancer. There was no significant difference in the measured outcomes between the two arms. The overall response rate at one month after radiotherapy was 88%, with 41% showing an improvement in motor outcomes and 47% no further progression. Seventy-three percent of patients were ambulant at one month after radiotherapy. There was no difference in local progression-free or overall survival.

An international multicentre retrospective study of 1034 patients with spinal cord compression[6] 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.[6] 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.

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2.34.1.3 Toxicity

The toxicity from these radiotherapy regimens is mild. Maranzano et al reported 1% Gd 3 oesophagitis, 0.5% Gd 3 pharyngeal dysphagia and 3% Gd 3 vomiting.[4] Rades et al reported no toxicities exceeding Grade 2 and no late toxicities, although specific toxicities were not listed.[5]

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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. Last reviewed November 2015	II	[4], [1], [5]

Evidence summary	Level	References
For patients treated with radiotherapy alone, lower radiotherapy doses (8Gy/1 fraction, 16Gy/2 fractions, 20Gy/5 fractions) have equivalent ambulatory and functional outcomes compared with higher radiotherapy doses. Last reviewed November 2015	II, III-2	[4], [6], [5]
Decompressive surgery in addition to radiotherapy may improve ambulatory and functional outcomes in selected patients with single level spinal cord compression. Last reviewed November 2015	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. Last reviewed November 2015	**B**

Evidence-based recommendation	Grade
Recommended radiotherapy doses for patients treated with radiotherapy alone are 8-20Gy in 1-5 fractions. Last reviewed November 2015	**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. Last reviewed November 2015

Practice point

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

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2.34.3 References

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2.35 First-line chemotherapy

Contents

2.35.1 What is the optimal first-line chemotherapy regimen in patients with stage IV inoperable NSCLC?

2.35.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

Prior to commencing first line systemic therapy, the histological subtype of the tumour should be established and adequate tissue obtained for molecular testing if possible. In particular, EGFR and ALK mutation testing should be performed and appropriate targeted therapy given instead of chemotherapy if one of these mutations is found.[1][2]

2.35.1.1.1 First-line chemotherapy

The first piece of evidence to establish a standard of practice was the meta-analysis of randomised trials until 1992 evaluating chemotherapy for non-Small Cell Lung Cancer by the Non-small Cell Lung Cancer Collaborative Group. Data from eight trials (N = 778) evaluating best supportive care versus best supportive care and cisplatin based chemotherapy showed a clear survival benefit in favour of chemotherapy with a hazard ratio of 0.73 (P<0.0001), or 27% reduction in the risk of death. This is equivalent to an absolute improvement in survival of 10% at one year, improving survival from 15% to 25%.

It is important to note that empirical chemotherapy has only been formally evaluated in "fit" patients. Patient performance status (PS) has conventionally been used to standardise and quantify cancer patient's general well-being and activities of daily life. The simplest of such scores in widespread use is the ECOG/WHO/ZUBROD score

WHO/ECOG/ZUBROD Performance Status Scale

0 – Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction)

1 – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and a work of a light or sedentary nature. For example, light housework, office work)

2 – Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry o activities. Up and about more than 50% of waking hours)

3 – Symptomatic, >50% in bed, but not bed-bound (Capable of only limited self-care, confined to bed or cha of waking hours)

4 – Bed-bound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)

5 – Death

[3]

By Convention, “fit” patients have a low PS and in most chemotherapy trials, the predominant patient group included is that with PS 0 or 1, with a minority being PS 2 or greater (referred to as poor performance status and described separately in the section below). Furthermore, chemotherapy trials have usually only included patients with adequate organ function and excluded patients with medically unstable co-morbidities and uncontrolled brain metastases.

A large number of randomised controlled studies and subsequent meta-analyses have been reported addressing questions such as, which platinum agent is best (carboplatin versus cisplatin)?; which new agent paired with a platinum agent is best (often referred to as "third generation (3G)” regimens)"?; is monotherapy with new (“3G”) agents as effective as platinum combination therapy?;are three chemotherapy agents (“triplet regimens”) better than two (“doublet regimens”)?; are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens?; what is the optimal duration of chemotherapy?; and is chemotherapy and a “biologic” or “targeted“ therapy superior to chemotherapy alone?

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2.35.2 Evidence summary and recommendations

Evidence summary	Level	References
Platinum-based chemotherapy improves survival in stage IV NSCLC compared with best supportive care. Note that this evidence is based on clinical trials conducted in fit patients, with predominant performance status 0-1, no unstable co-morbidities, adequate organ function and without uncontrolled brain metastases. Last reviewed December 2015	I	[4], [5]

Evidence-based recommendation	Grade
Platinum-based chemotherapy can be used to extend survival in newly diagnosed patients with stage IV NSCLC. Last reviewed December 2015	**A**

Practice point

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.

Last reviewed December 2015

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2.36 Carboplatin vs cisplatin

Contents

2.36.1 Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC?

2.36.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.36.1.1.1 Carboplatin versus cisplatin

Three meta-analyses have addressed the question of whether carboplatin based chemotherapy is as effective as cisplatin based,[1][2][3] which collectively confirm that cisplatin based regimens are associated with a slightly higher response rate than carboplatin regimens, with no definite survival difference.The first meta-analysis by Hotta et al, evaluated 2948 patients from eight randomised controlled trials (RCTs) from 1990-2004.[1]. Cisplatin-based chemotherapy produced a higher response rate (RR), but overall survival (OS) was not significantly different.[1] The second, by Ardizzoni et al, was an individual patient data meta-analysis of 2968 patients from nine RCTs from 1990 to 2004. This study found that objective RR was higher for patients treated with cisplatin than for patients treated with carboplatin (30% versus 24%, respectively; Odds ratio (OR) = 1.37; 95% CI = 1.16 to 1.61; P <.001).[2] There was no overall difference in mortality, however, as in the Jiang meta-analysis, a subset analysis of survival in five trials evaluating “new” agents (gemcitabine, docetaxel, paclitaxel and vinorelbine) found OS with carboplatin slightly inferior to cisplatin (hazard ratio (HR) = 1.12; 95% CI = 1.01 to 1.23).[2] Cisplatin-based chemotherapy was associated with more severe nausea and vomiting and nephrotoxicity; severe thrombocytopaenia was more frequent during carboplatin-based chemotherapy.[2] Jiang et al, evaluated published data from 6906 patients from 18 RCTs from 1990-2006.[3] This study confirmed the findings of Hotta and Arziddoni with regard to RR in favour of cisplatin, however it did not find any survival difference in eight studies evaluating the new agents above.[3]

The question of whether to use cisplatin versus carboplatin is of lower significance today especially given the new information arguing in favour of selecting specific treatments for greater benefit by histology and the presence of activating gene mutations.

2.36.2 Evidence summary and recommendations

Evidence summary	Level	References
	I	[1], [2], [3]

Evidence summary	Level	References
First-line chemotherapy involving cisplatin results in a slightly higher likelihood of tumour response than the same chemotherapy with carboplatin. Last reviewed December 2015		
There is no definite overall survival difference between cisplatin or carboplatin based first-line chemotherapy. Last reviewed December 2015	I	[1], [2], [3]
Cisplatin-based chemotherapy is associated with more severe nausea and vomiting and nephrotoxicity; severe thrombocytopaenia is more frequent during carboplatin-based chemotherapy. Last reviewed December 2015	I	[1], [2], [3]

Evidence-based recommendation	Grade
In patients with high tumour burden and symptoms from stage IV NSCLC cisplatin based 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. Last reviewed December 2015	**B**

Practice point
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. Last reviewed December 2015

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2.36.3 References

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2.37 Optimal new agent or platinum combination regimen

Contents

2.37.1 Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC?

2.37.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.37.1.1.1 New agent or platinum combination regimens

Several meta-analyses and numerous RCTS have evaluated this question either as their primary endpoint or as part of secondary analyses. New agents making up so – called “third generation” regimens include gemcitabine, vinorelbine, docetaxel, paclitaxel and irinotecan.[1][2][3][4]

Baggstrom et al, meta-analysed results from twelve RCTs from 1994 – 2004 (n= 3995 patients) comparing response rate (RR) and overall survival (OS) with 3G combination regimens including platinum-based compounds with second generation (2G) platinum-based regimens.[1] The estimated absolute risk difference (RD) in RR in favour of 3G regimens was 12% (95% CI: 10 -15%), corresponding to a number need to treat (NNT) of eight for one patient to benefit.[1] Owing to a high degree of heterogeneity across the studies, analysis of OS could not be undertaken.

Grossi et al, evaluated the relative impact of different 3G drugs (vinorelbine, gemcitabine, paclitaxel, docetaxel) on the activity of first-line chemotherapy in advanced NSCLC by considering RR and progressive disease (PD), in 45 RCTs (N = 11,867 patients).[3] They found the odds of obtaining an objective response to treatment similar across the different regimens. Different rates of disease control were observed, with gemcitabine chemotherapy associated with a significant 14% lower risk for immediate progression, whereas patients receiving paclitaxel-based treatment appear to be at a higher risk for having PD as their best response.[3] However, OS was not assessed in this meta-analysis.

Gao et al, examined whether platinum plus gemcitabine or vinorelbine are equally effective in the treatment of advanced NSCLC.[2] This publication only meta-analysis evaluated nine RCTs involving 2186 patients, and found that no differences in RR or one-year OS.[2] Vinorelbine plus platinum regimens led to more frequent grade 3 or 4 neutropaenia, nephrotoxicity, constipationand phlebitiswhile gemcitabineplus platinum chemotherapy was associated with more grade 3 or 4 thrombocytopaenia.[2]

These meta-analyses collectively confirm better RR with 3G regimens compared with 2G but with differing toxicity profiles across the regimens and uncertainty or no difference in OS. A RCT of 1155 patients, evaluating four commonly used 3G platinum based regimens (vinorelbine, docetaxel, paclitaxel and gemcitabine) similarly failed to demonstrate superiority (in OS and RR) of one regimen over another although toxicity differences were observed.[4]

In the setting of first-line empirical chemotherapy, the study by Scagliotti et al compared the effectiveness of cisplatin and pemetrexed to cisplatin and gemcitabine in a RCT of 1,725 patients.[5] This study confirmed non-inferiority of cisplatin/pemetrexed compared with cisplatin/gemcitabine for the overall population, but also confirmed (in pre-planned analyses), superiority of cisplatin/pemetrexed for OS compared with cisplatin /gemcitabine in patients with non-SCC histology (HR 0.81, 95% CI 0.70 - 0.94), with median OS 12.6 versus 10.9 months for adenocarcinoma histology (n = 847, and 10.4 versus 6.7 months for large cell carcinoma (n = 153). [5] Conversely, in patients with SCC, there was a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (n = 473; median OS 10.8 versus 9.4 months, respectively, HR 1.23 (95% CI 1.00 – 1.51, p = 0.05)). For cisplatin/pemetrexed, rates of grade 3/4 neutropaenia, anaemia, and thrombocytopaenia (p = 0.001); febrile neutropaenia (p = 0.002); and alopecia (p = 0.001) were significantly lower, whereas grade 3 or 4 nausea (p = 0 .004) was more common.

Gronberg et al compared carboplatin/pemetrexed to carboplatin/gemcitabine in a RCT of 436 patients with the primary endpoint of health-related quality of life.[6] Compliance with completion of health-related QOL questionnaires was 87%. There were no significant differences for the primary health-related QOL endpoints, or in OS between the two treatment arms (pemetrexed/carboplatin, 7.3 months; gemcitabine/carboplatin, 7.0 months; P=0.63). Multivariate analyses and interaction tests did not reveal any significant associations between histology and survival. As in the Scagliotti study, rates of Grade ¾ haematologic toxicity were less with carboplatin/pemetrexed.[6]

2.37.2 Evidence summary and recommendations

Evidence summary	Level	References
3G platinum-based chemotherapy (vinorelbine, paclitaxel, docetaxel or gemcitabine) is associated with higher response ratio than older 2G platinum-based chemotherapy. Last reviewed September 2017	I	[1], [2], [3]
No 3G platinum-based chemotherapy regimen (vinorelbine, paclitaxel, docetaxel or gemcitabine) has been shown to be superior to another. Last reviewed September 2017	I	[1], [2], [3]
	II	[5]

Evidence summary	Level	References
In first-line empirical treatment of advanced NSCLC, chemotherapy with cisplatin and pemetrexed is superior to cisplatin/gemcitabine in patients with non-squamous cell carcinoma histology. Last reviewed September 2017		
In first-line empirical treatment of advanced NSCLC, chemotherapy with cisplatin and pemetrexed is inferior to cisplatin/gemcitabine in patients with SCC histology. Last reviewed September 2017	II	[5]

Evidence-based recommendation	Grade
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. Last reviewed September 2017	**A**

Evidence-based recommendation	Grade
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. Last reviewed September 2017	**B**

Evidence-based recommendation	Grade
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. Last reviewed September 2017	**B**

Practice point

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.

Last reviewed September 2017

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2.37.3 References

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2. ↑ 2.0 2.1 2.2 2.3 2.4 2.5 Gao G, Jiang J, Liang X, Zhou X, Huang R, Chu Z, et al. *A meta-analysis of platinum plus gemcitabine or vinorelbine in the treatment of advanced non-small-cell lung cancer.* Lung Cancer 2009 Sep;65(3):339-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19144444.
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5. ↑ 5.0 5.1 5.2 5.3 Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. *Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.* J Clin Oncol 2008 Jul 20;26(21):3543-51 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18506025.
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2.38 Monotherapy with new 3G agent vs platinum combination therapy

Contents

2.38.1 Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC?

2.38.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.38.1.1.1 Monotherapy with new agents versus platinum combination therapy

A meta-analysis by Hotta et al, examined the question of how treatment with single agent 3G agents (vinorelbine, paclitaxel, docetaxel, gemcitabine and irinotecan) compares with the same agent and a platinum agent.[1] This meta-analysis evaluated 2374 patients from eight RCTs between 1994 – 2003. A greater than two-fold higher overall response rate (RR) was seen with platinum combination than the new agent alone [odds ratio = 2.32; 95% CI 1.68–3.20]. Platinum-based doublet therapy was associated with a 13% prolongation of overall survival (OS) (HR = 0.87; 95% CI = 0.80–0.94,P <0.001).[1] Despite significant increases in the frequencies of various toxicities in patients receiving platinum-based doublets, no significant difference in treatment-related mortality was observed.[1]

Baggstrom et al in their meta-analsysis examined the effectiveness of 3G agents (vinorelbine, paclitaxel, docetaxel and gemcitabine) as first-line monotherapy compared with best supportive care in five RCTS of 1029 patients from 1996 – 2000.[2] One trial used 5-fluorouracil (5FU)/leucovorin as the control arm. RR for the 3G regimens ranged from 12-20%. One-year survival favored the 3G agents over best supportive care with a summary absolute risk difference of 7% (95% CI: 2 - 12%). They calculated that the NNT for one patient to realise a benefit in the probability of one-year survival was 14.

Delbaldo et al examined the effectiveness of two-drug platinum combination chemotherapy compared with single agent therapy.[3][4] This study evaluated 7175 patients from 29 RCTs but also included studies using older agents such as etoposide, vindesine and mitomycin C, as well as the modern 3G agents previously listed. Some of the studies included used a non-platinum combination in the comparator arm. Two-drug combination therapy was found to have a higher RR (OR, 0.42; 95% CI 0.37-0.47; p <.001). The absolute benefit was 13%, which corresponds to a two-fold increase in RR from 13% with a single-agent regimen to 26% with a doublet

regimen.[4] The benefit was higher when the control arm was an older drug (OR, 0.35) than when it was a newer drug (OR, 0.52) (P=.001). Two-drug combination therapy was associated with a significant increase in one-year survival (OR, 0.80; 95% CI, 0.70-0.91; P<.001)[4] The absolute benefit was 5%, which corresponds to an increase in one-year survival from 30% with a single agent regimen to 35% with a doublet regimen. The benefit was higher when the control arm was an older drug than newer drug for both one-year survival rate (p=.03) and median survival (p=.007).[4]

2.38.2 Evidence summary and recommendations

Evidence summary	Level	References
3G platinum-based combination chemotherapy (vinorelbine, paclitaxel, docetaxel, irinotecan or gemcitabine) is superior to 3G agent monotherapy. Last reviewed December 2015	I	[1], [4]
3G platinum-based monotherapy (vinorelbine, paclitaxel, docetaxel, or gemcitabine) improves survival compared with best supportive care. Last reviewed December 2015	I	[2]

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**A**

Evidence-based recommendation	Grade
Patients unfit for combination chemotherapy could be considered for 3G monotherapy with vinorelbine, paclitaxel, docetaxel or gemcitabine. Last reviewed December 2015	**A**

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2.38.3 References

1. ↑ 1.0 1.1 1.2 1.3 Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. *Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials.* J Clin Oncol 2004 Oct 1;22(19):3860-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15326194.
2. ↑ 2.0 2.1 Baggstrom MQ, Stinchcombe TE, Fried DB, Poole C, Hensing TA, Socinski MA. *Third-generation chemotherapy agents in the treatment of advanced non-small cell lung cancer: a meta-analysis.* J Thorac Oncol 2007 Sep;2(9):845-53 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17805063.
3. ↑ Delbaldo C, Michiels S, Syz N, Soria JC, Le Chevalier T, Pignon JP. *Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis.* JAMA 2004 Jul 28;292(4):470-84 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15280345.
4. ↑ 4.0 4.1 4.2 4.3 4.4 Delbaldo C, Michiels S, Rolland E, Syz N, Soria JC, Le Chevalier T, et al. *Second or third additional chemotherapy drug for non-small cell lung cancer in patients with advanced disease.* Cochrane Database Syst Rev 2007 Oct 17;(4):CD004569 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17943820.

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2.39 Three vs two chemotherapy agents

Contents

2.39.1 Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC?

2.39.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here The focus of the following question will be based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.39.1.1.1 Triplet regimens versus doublet regimens

Delbaldo et al also examined the effectiveness of three-drug combination chemotherapy compared with two-drug combination chemotherapy.[1] This study evaluated 4814 patients from 28 RCTs.Adding a third drug to a doublet regimen was associated with a significantly increased response rate (RR) (OR, 0.66; 95%CI, 0.58-0.75; p <.001).[1] The absolute benefit was 8%, which corresponds to an increase in tumour RR from 23% (doublet regimen) to 31% (triplet regimen).[1] There was no difference in RR whether the doublet regimens contained older or newer (3G) drugs (p=0.33). Adding a third drug to a doublet regimen did not improve one-year survival (OR, 1.01;95% CI, 0.85-1.21; P=0.88) and there was no significant difference according to the type of control regimens used (older drugs versus newer (3G) drugs) for both one-year survival rate (p =.28) and median survival (p =.36).[1] However, grade ¾ toxicity was more common in triplet regimens than in doublet regimens with ORs ranging from 1.4 to 2.9,except for neurological, renal, auditory and gastrointestinal toxic effects.[1]

2.39.2 Evidence summary and recommendations

Evidence summary	Level	References
Triplet chemotherapy regimens are associated with higher response rate, but no improvement in survival. Last reviewed December 2015	I	[1]
Triplet chemotherapy regimens are associated with greater grade 3 /4 toxicities. Last reviewed December 2015	I	[2]

Evidence-based recommendation	Grade
Triplet chemotherapy regimens are not recommended, as benefit in response rate does not outweigh extra toxicity. Last reviewed December 2015	**A**

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2.40 Non-platinum doublet vs platinum doublet regimen

Contents

2.40.1 Are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens for treatment of stage IV inoperable NSCLC?

2.40.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.40.1.1.1 Doublet chemotherapy regimens versus platinum doublet regimens

D'Addario et alevaluated this question in a meta-analysis of 7633 patients from 37 RCTs between 1983 and 2002.[1] Platinum-based therapy was associated with a 62% increase in the odds ratio (OR) for response rate (RR) (OR, 1.62; 95% CI,1.46 =1.8; P <.0001). The one-year overall survival (OS) was increased by 5% with platinum-based regimens (34% versus 29%; OR, 1.21; 95% CI, 1.09 to 1.35; P =.0003).[1] However, no statistically significant increase in one-year survival was found when platinum therapies were compared to 3G – based combination regimens (OR, 1.11; 95% CI, 0.96 to 1.28; P = .17).[1] The toxicity of platinum-based regimens was significantly higher for hematologic toxicity,nephrotoxicity, and nausea and vomiting, but not for neurotoxicity, febrile neutropaenia rate,or toxic death rate.[1]

Rajeswaran et al also evaluated this question in a meta-analysis of 4920 patients from 17 RCTs.[2] Platinum based doublet regimens were associated with a slightly higher one-year survival (RR = 1.08, 95% CI 1.01—1.16, p = 0.03), a greater response rate (RR = 1.11, 95% CI 1.02—1.21, p = 0.02), but with a higher risk of anaemia, nausea, and neurotoxicity.[2] Cisplatin-based doublet regimens improved one-year survival (RR = 1.16, 95% CI 1.06-1.27, p = 0.001), complete response. (RR = 2.29, 95% CI 1.08-4.88, p = 0.03), and partial response (RR = 1.19, 95% CI 1.07-1.32, p = 0.002), but with an increased risk of anaemia, neutropaenia, neurotoxicity and nausea.[2] Conversely, carboplatin based doublet regimens did not increase one-year survival (RR = 0.95, 95% CI 0.85—1.07,p = 0.43). However, although carboplatin-based doublet regimens were associated with higher risk of anaemia and thrombocytopaenia, there was no increased nausea and/or vomiting.[2]

Li et al compared the activity, efficacy, and toxicity of gemcitabine plus paclitaxel versus carboplatin plus either gemcitabine or paclitaxel in 2186 patients with untreated advanced NSCLC from four RCTSs.[3] A significant difference in RR favouring gemcitabine plus paclitaxel over carboplatin-based doublets was observed [OR = 1.20; 95% CI 1.02–1.42; P = 0.03], whereas the trend toward an improved one-year OS was not significant (OR = 1.07; 95% CI = 0.91–1.26; P = 0.41).[3] An increased risk of grade 3/4 toxicities for patients receiving carboplatin-based chemotherapy was demonstrated.[3]

2.40.2 Evidence summary and recommendations

Evidence summary	Level	References
Platinum-based doublet 3G chemotherapy is associated with a higher response rate and slightly higher one-year survival than non-platinum doublet chemotherapy. Last reviewed December 2015	I	[1], [2], [3]
Platinum-based doublet 3G chemotherapy is associated with greater risk of anaemia and thrombocytopaenia than non-platinum combination therapy. Last reviewed December 2015	I	[1], [2], [3]
Gemcitabine and paclitaxel improves response ratio without added toxicity, compared with gemcitabine or paclitexel and carboplatin combinations. Last reviewed December 2015	I	[3]

Evidence-based recommendation	Grade
Non-platinum 3G doublet chemotherapy is an effective alternative option for patients unsuitable for platinum-based therapy. Last reviewed December 2015	**B**

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2.41 Optimal duration of first-line chemotherapy

Contents

2.41.1 What is the optimal duration of first-line chemotherapy for treatment of stage IV inoperable NSCLC?

2.41.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.41.1.1.1 Duration of first-line chemotherapy

By convention, many clinical trials evaluating chemotherapy in stage IV NSCLC capped treatment to a maximum of six cycles, often being limited due to toxicity. Efficacy assessments usually occurred after the second or third chemotherapy cycle at six to eight weekly intervals. Although several small randomised controlled trials (RCTs) have been conducted addressing the question of duration of treatment, there is a great deal of heterogeneity in the design of these studies in terms of the treatment regimens used, the scheduling and duration of chemotherapy being explored. Two systematic reviews have attempted to address the optimal duration of chemotherapy [1][2].

The study by Soon et al was designed to determine the effects of extending chemotherapy beyond a standard number of cycles. It evaluated 3,027 patients from 13 RCTs comparing a defined number of cycles with continuation of the same chemotherapy until disease progression, a larger defined number of cycles of identical chemotherapy, RCTs comparing a defined number of cycles of identical initial chemotherapy followed by additional cycles of an alternative chemotherapy.[1]

The key findings were that extending chemotherapy appeared to significantly improve progression free survival (PFS; HR0.75; 95% CI: 0.69 -0.81; p < .00001) whereas the effect on overall survival (OS) was modest and less certain (HR, 0.92; 95% CI: 0.86 - 0.99; P < .03).[1] Subgroup analysis revealed that the effects on PFS were greater for trials extending chemotherapy with 3G regimens rather than older regimens (P < .003).[1] Extending chemotherapy was associated with more frequent adverse events in all trials where it was reported and impaired health related quality of life (QOL) in two of seven trials.[1]

The study by Lima et al was designed to determine the effects of continuing first-line chemotherapy. It evaluated 1559 patients from seven RCTs (included in the Soon meta-analysis) comparing different durations of first-line treatment of advanced NSCLC[2]. Treatment for more than four cycles was not associated with a decrease in mortality relative to shorter treatment (HR = 0.97; 95% CI = 0.84 - 1.11; P = 0.65)[2]. Patients receiving more chemotherapy had significant longer progression-free survival (HR = .75; 95% CI = 0.60 – 0.85; P < 0.0001) than the group with shorter duration of treatment, but there was no difference in response rate (RR) and longer treatment was associated with more severe leucopaenia, although non-haematological toxicities were not significantly increased[2].

The study by Lima et al more closely addressed the question of duration of first line chemotherapy, whereas the study by Soon et al, focused on whether more chemotherapy is better than a fixed amount. It, however, contains a more heterogeneous mix of studies with a greater variety of regimens, including regimens not in use (involving alkylating agents). However, the overall study findings are not changed with the inclusion of these individual studies[1]. Both studies agree in the finding that PFS is prolonged with longer chemotherapy however, a consistent improvement in overall survival was not observed. Given the toxicity associated with standard first-line chemotherapy, it appears reasonable to stop after four cycles of treatment. Continuing the same first line treatment beyond this should be individually based and consider the evidence for continuation or switch maintenance therapy discussed in detail in the section below.

2.41.2 Evidence summary and recommendations

Evidence summary	Level	References
Extending the duration of first-line combination chemotherapy beyond four cycles of chemotherapy, in non-progressive patients, improves progression free survival but not overall survival, and at the expense of increased toxicity and potentially reduced quality of life. Last reviewed December 2015	I	[2], [1]

Evidence-based recommendation	Grade
First-line combination chemotherapy should in most cases be stopped at disease progression or after four cycles in patients with advanced NSCLC. Last reviewed December 2015	**B**

Practice point
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. Last reviewed December 2015

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2.41.3 References

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2.42 Chemotherapy with biologic or targeted therapy vs chemotherapy alone

Contents

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?

2.42.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

Numerous trials have been reported over the years exploring the benefit of adding novel drug therapy to standard chemotherapy. This section will review the evidence for benefit or lack thereof, of the addition of modern biologic or targeted therapy to standard first-line chemotherapy as empirical therapy in “selected" or "unselected" patients. Biologic therapy refers to monoclonal antibodies (MAbs) and will be summarised by the specific MAb target. Molecularly targeted therapy refers to therapy given to patients selected exclusively by the presence of a particular gene or its protein product identified as the specific drug target.

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2.42.1.1.1 Chemotherapy and AIs - anti-VEGF Mab (bevacizumab) or anti-VEGF TKIs

There have been two phase III and one phase II RCT of chemotherapy +/- bevacizumab as first-line therapy in patients with stage IV NSCLC.[1][2][3] The first study, a randomised phase II study by Johnston et al showed promising activity with bevacizumab but found an unexpectedly high incidence of pulmonary haemorrhage in patients with SCC.[3] The study by Sandler et al examined carboplatin and paclitaxel +/- bevacizumab, whilst the study by Reck et al examined cisplatin and gemcitabine +/- bevacizumab.[1][2] Consequently both

subsequent PIII studies excluded patients with the following: SCC histologic type, brain metastases, clinically significant hemoptysis,inadequate organ function, ECOG PS of 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension. The overall safety and efficacy of chemotherapy and bevacizumab has been summarised in a meta-analysis of four trials with 2101 patients by Yang et al.[4] Bevacizumab has been studies at high dose (HD: 15 mg/kg) or low dose (LD: 7.5 mg/kg) every three weeks with chemotherapy.

Yang et al found that neither HD or LD bevacizumab improved one-year survival when added to chemotherapy.[4] However, the addition of HD bevacizumab increased two-year overall survival (OS) (RR 1.24; 95% CI 1.04 – 1.49) and tumour response rate (RR 1.69; 95% CI 1.21-2.35).[4] However in an independent systematic review by Botrel et al, although an OS benefit was observed with HD bevacizumab (HR 0.89, 95% CI 0.8 – 1.0, p =0.04), there was moderate statistical heterogeneity (Chi2 = 5.09, 3df, p = 017; I2 = 41%), making this finding less certain. Progression free survival (PFS) was improved with both LD bevacizumab (HR 0.76; 95%; CI 0.64-0.90) and HD bevacizumab (HR 0.73; 95%CI 0.65-0.81).[4][5] However, HD bevacizumab was associated with an increase in treatment related deaths (RR 2.07, 95%; CI 1.19-3.59). Patients treated with HD bevacizumab experienced more hypertension, headaches, haemoptysis, neutropaenia and rash than patients on chemotherapy alone.[4] In the phase III trials bevacizumab was continued if tolerated until disease progression.

With regard to the small molecule TKIs, numerous phase III studies have been conducted but only one study has been published in full to date. Scagliotti et al, reported the outcomes of their phase III RCT evaluating the efficacy and safety of sorafenib, in combination with carboplatin and paclitaxel in chemotherapy-naïve patients.[6] The study was terminated after the interim analysis concluded that the study was highly unlikely to meet its primary end point for OS. A pre-specified exploratory analysis revealed that patients with squamous cell histology had greater mortality in arm A than in arm B (HR 1.85; 95%; CI 1.22 to 2.81).

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2.42.1.1.2 Chemotherapy and anti-EGFR TKIs

Following the discovery of the first generation EGFR TKIs gefitinib and erlotinib, four first-line placebo controlled RCTS were undertaken, evaluating the efficacy of the addition of these agents to two commonly used chemotherapy regimens (carboplatin/paclitaxel and cisplatin/gemcitabine)[7][8][9][10] In all four trials the addition of the EGFR TKIs, gefitinib or erlotinib to a standard chemotherapy regimen did not improve outcomes (OS, RR or time to progression (TTP) compared with chemotherapy alone.

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2.42.1.1.3 Chemotherapy and anti-EGFR with the Mab cetuximab

The first monoclonal antibody to EGFR to enter the clinic was cetuximab. Two meta-analyses have summarised the evidence for the addition of cetuximab to standard chemotherapy, from four RCTs with 2018 patients with advanced NSCLC (selected by the presence of EGFR-positive tumor as measured by immunohistochemistry (IHC), two of which were phase III RCTs.[11][12][13][14] Both meta-analsyses concur in finding that overall survival was improved by the addition of cetuximab to chemotherapy (HR 0.87; 95%CI, 0.79–0.96; p = 0.004)[12] and overall response rate was increased (50% increase (odds ratio (OR) = 1.48; (CI = 1.22–1.80); p < 0.0001). PFS

whilst improved with the addition of cetuximab to chemotherapy was not significantly better than chemotherapy alone (HR, 0.91; 95%CI, 0.83–1.00; p = 0.06).[11][12] Of the two Phase III trials, only the Pirker study which added cetuximab to cisplatin/vinoerlbine was positive for survival, whilst the Lynch study, which added cetuximab to carboplatin/paclitaxel showed improved RR but not PFS or OS.[13][14] The addition of cetuximab was associated with increased grade 3/4 rash and infusion reactions.[11][12] In the phase III trials cetuximab was continued if tolerated until disease progression.

2.42.2 Evidence summary and recommendations

Evidence summary	Level	References
In carefully selected** patients with advanced NSCLC, high dose bevacizumab improves tumour response rate and progression free survival. **Patients with the following criteria were excluded from the trials: SCC histologic type, brain metastases, clinically significant haemoptysis,inadequate organ function, ECOG PS of 1, therapeutic anticoagulation, clinically significant cardiovascular disease, or medically uncontrolled hypertension. Last reviewed December 2015	I	[4], [5]
In carefully selected** patients with advanced NSCLC, treatment with high dose bevacizumab is associated with an increase in treatment related deaths. Last reviewed December 2015	I	[4]

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**B**

Evidence summary	Level	References
The addition of the EGFR TKIs gefitinib or erlotinib to a standard chemotherapy regimen does not improve outcomes (OS, RR or time to progression (TTP)) compared with chemotherapy alone. Last reviewed December 2015	II	[7], [8], [10], [9]

Evidence-based recommendation	Grade
The first generation EGFR TKIs gefitinib or erlotinib should not be used in unselected patients in combination with standard chemotherapy. Last reviewed December 2015	**A**

Evidence summary	Level	References
In patients with advanced NSCLC (selected by the presence of EGFR-positive tumour as measured by immunohistochemistry), the addition of cetuximab to chemotherapy increases response rate and improves overall survival. This overall benefit was modest and observed only in the phase III trial using cisplatin/vinorelbine . Last reviewed December 2015	I	[11], [12]

Evidence-based recommendation	Grade
In patients with advanced NSCLC 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. Last reviewed December 2015	**B**

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2.43 Optimal chemotherapy for overall QoL

Contents

2.43.1 What is the optimal chemotherapy regimen for overall quality of life for patients in the treatment of stage IV inoperable NSCLC?

2.43.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.43.1.1.1 Different chemotherapy regimens and health related quality of life

Many of the aforementioned clinical trials have formally included patient rated QOL evaluation usually as a secondary endpoint. The overall effect of common chemotherapy regimens on health related QOL in NSCLC is probably best summarised in the meta-analysis by Tanvetyanon et al.[1] This study identified 14 RCTs from 1998 – 2005 with 6665 patients to determine differences in QOL between the regimens studies. Of these, 13 trials using a validated QOL instrument were included for review. The meta-analsysis found QOL reporting /analysis techniques were heterogeneous. Nine RCTs reported the rate of completedbaseline assessment and compliance survivors at analysis of greaterthan 50%, for data synthesis.[1] Of these, only one trial found a significant difference in QOL between the comparator arms: paclitaxelplus cisplatin was better than teniposide plus cisplatin. However, teniposide is not used in practice today. Based on this review, it seems unlikely that a major difference exists in the global QOL associated with standard chemotherapy regimens for advanced NSCLC.[1] Furthermore, the authors concluded that although the available QOL reporting formats are largely acceptable, a lack of uniformity in analysis and a poor compliance to QOL assessment made between-trial comparisons difficult.[1]

A large single RCT of 926 patients (not included in the Tanvetyanon meta-analysis[1]) comparing docetaxel and cisplatin (DC) or carboplatin (DCb) with cisplatin /vinorelbine (VC) also examined QOL using the Lung Cancer Symptom Scale (LCSS) and the general EuroQol five-dimensional questionnaire (EQ-5D).[2] DCband DC were superior to VC in the QoL outcomes assessed except for the difference between DC and VC in LCSS ‘‘QOL today’’, which was not significant.[2]

There does not appear to be any major difference evident in the global quality of life associated with standard chemotherapy regimens for advanced NSCLC.[1]

2.43.2 Evidence summary and recommendations

Practice point

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.

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2.44 Optimal first-line maintenance therapy

Contents

2.44.1 What is the optimal first-line maintenance therapy for treatment of stage IV inoperable NSCLC?

2.44.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.44.1.1.1 First-line maintenance therapy

"Maintenance" therapy, described in detail here refers to the concept of continuing drug therapy until progression. Maintenance treatment can be further characterised by continuing part of the initial treatment regimen (usually the new generation regimen whilst stopping the platinum) - this is referred to as "continuation maintenance" or by switching after disease control with an initial combination therapy to another agent - this is referred to as "switch maintenance".

There have been nine studies conducted formally addressing the question of maintenance therapy in advanced NSCLC, eight of which were evaluated in a systematic review by Zhang et al, with the most recent RCT of maintenance pemetrexed after induction pemetrexed/platinum therapy reported in 2011 but not yet published.[1][2] Zhang et al undertook a systematic review of eight trials (3, 736 patients) investigating maintenance therapy with either a continuous or a switch strategy for patients with non-progressing NSCLC compared with placebo or observation with overall survival (OS) as the primary outcome.[1] Another study not included in the meta-analysis by Zhang evaluated the role of maintenance carboxyaminotriazole (CAI) in patients with advanced NSCLC with non-progression after initial chemotherapy. CAI was a novel but unproven therapy, demonstrated to modulate tumour cell motility, adhesion and angiogenesis. Unfortunately no benefit was observed compared to placebo.[3]

Three studies were identified evaluating continuation maintenance with gemcitabine whilst the switch maintenance studies included in this meta-analysis evaluated either docetaxel, pemetrexed, erlotinib, erlotinib and bevacizumab, or gefitinib.[1] Zhang et al found that the concept of switch maintenance therapy substantially improved OS compared with placebo or observation (hazard ratio [HR], 0.85; 95% CI, 0.79-0.92; P , .001). However, gemcitabine as continuous maintenance therapy, did not statistically improve survival (HR, 0.88; 95% CI, 0.74-1.04; P = 0.124).[1] Subgroup analyses showed benefits of switch maintenance therapy with both cytotoxic agents (docetaxel/pemetrexed studies combined) (HR, 0.80; 95% CI, 0.69-0.93; P 5 .003) and EGFR TKI-targeted agents (gefitinib/erlotinib studies combined) (HR, 0.87; 95% CI, 0.80-0.95; P 5 .001).[1] Clinically and statistically significant improvement in PFS was found with both maintenance strategies (switch maintenance therapy HR, 0.67; 95% CI, 0.57-0.78; continuous maintenance therapy HR, 0.53; 95% CI, 0.43-0.65; interaction P = 0.128).[1]

The meta-analysis by Zhang et al thus confirmed in principle that there is benefit from the concept of maintenance therapy in NSCLC, with OS benefit observed in switch maintenance approach and PFS benefit from both switch and continuous maintenance approaches. Of the studies included in the meta-analysis by Zhang et al, the three positive published studies are of switch maintenance using docetaxel, pemetrexed or erlotinib.[4][5][6] These are discussed in more detail below to determine the benefits and harms of each approach for the purposes of providing a more specific practice guideline.

The first study by Fidias et al, compared immediate with delayed docetaxel after first-line therapy with gemcitabine and carboplatin in 309 patients with advanced NSCLC.[4] Patients were randomised to immediate versus delayed docetaxel if they were stable after four cycles of induction chemotherapy. The primary endpoint of OS was not significantly different (p = 0.085) even though there was a trend in median OS in favour of immediate docetaxel (12.3 months versus 9.7 months (delayed)).[4] However, PFS was significantly longer for immediate docetaxel (5.7 months) than for delayed docetaxel (2.7 months) (P .0001), and QOL results were not statistically different (P= 0.76) between docetaxel groups.[4]

The second study by Ciuleanu et al, randomised 663 patients who had not progressed after four cycles of first-line platinum-based chemotherapy to pemetrexed or placebo.[5] The primary endpoint of the study was PFS. Pemetrexed was shown to significantly improve PFS (4.3 months [95% CI 4.1–4.7] versus 2.6 months [1.7–2.8]; HR 0.50, 95% CI 0.42–0.61, p<0.0001) and also improve OS (13.4 months [11.9–15.9] versus 10.6 months [8.7–12.0]; HR 0.79, 0.65–0.95, p=0.012) compared with placebo.[5] These benefits were mainly in patients with non-SCC histology (PFS HR 0.44; (95% CI 0.36–0.55); and OS HR 0.70; (95% CI 0.56–0.88). compared with squamous histology (PFS HR 069, 95% CI 0.49–0.98); and OS HR 1.07, (95% CI 0.77–1.50).[5] In the non-SCC population, the benefit with pemetrexed was most certain in the adenocarcinoma (PFS HR 0.51 (0.38–0.68); <0.0001, and OS HR 0.73 (0.56–0.96); 0.026) and other NSCLC sub-groups. This observation was confirmed by a significant treatment-by-histology interaction with both PFS (p=0036) and OS (p=0033).[5] Drug-related grade three or higher toxic effects were higher with pemetrexed than with placebo (mainly fatigue and neutropaenia).[5]

The final study, by Capuzzo et al, randomised 884 patients who had not progressed after four cycles of first-line platinum-based chemotherapy were randomised to erlotinib 150 mg daily or placebo. The co-primary endpoints were PFS in all patients irrespective of EGFR status, and PFS in patients whose tumours had EGFR protein over-expression, as determined by IHC.[6] Median PFS was signifi cantly longer with erlotinib than with placebo: 12.3 weeks (erlotinib) versus 11.1 weeks (placebo) group (HR 0.71, 95% CI 0.62–0.82; p<0.0001). PFS was also significantly longer in patients who were EGFR IHC positive and treated with erlotinib (n=307) compared with EGFR-positive patients given placebo (n=311; median PFS 12.3 weeks (erlotinib) versus 11.1 weeks (placebo); HR 0.69, 0.58–0.82; p<0.0001).[6] A pre-planned analysis of PFS in patients with EGFR-activating mutations confirmed a substantial benefit (HR 0.10, 95% CI 0.04 – 0.25; p<0.0001;) but also benefit, albeit more modest, in patients with wild-type EGFR (HR 078, 95% CI 0.63–0.96; p=0.0185).[6] Overall survival was significantly prolonged with erlotinib versus placebo in the intention-to-treat population (median 12.0 versus 11.0 months; HR 0.81, 95% CI 0.70–0.95; p=0.0088).[6] The commonest grade 3 or higher toxicities associated with erlotinib were rash (9%) and diarrhea (2%).[6]

Taken collectively and allowing for differences in study design, all three studies indicated benefit in unselected patients from this “switch maintenance” approach of immediate alternative treatment with single agent docetaxel, pemetrexed or erlotinib, by significantly delaying progression free survival (PFS), and in the cases of erlotinib and pemetrexed in non-SCC histology, also improving OS. In each study, the treatment switch was evaluated only in patients with stable disease or response after four cycles of standard first-line chemotherapy. In the case of pemetrexed, the benefit appears to be in the non-SCC histology sub-group. In the case of patients with known EGFR-gene activating mutations, switch maintenance erlotinib provides substantial benefit.

2.44.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients with stable or responsive advanced NSCLC after initial platinum doublet chemotherapy, the principle of switch maintenance therapy to either chemotherapy or anti-EGFR TKI improves overall survival. Last reviewed December 2015	I	[1]
In patients with stable or responsive advanced NSCLC after four cycles of initial platinum doublet chemotherapy, both approaches of switch maintenance and continuation maintenance improves progression free survival. Last reviewed December 2015	I	[1]
In patients with stable or responsive advanced NSCLC after four cycles of initial carboplatin/gemcitabine chemotherapy, immediate docetaxel prolongs progression free survival compared with delaying treatment for relapse, without decreasing quality of life. Last reviewed December 2015	II	[4]
In patients with stable or responsive advanced NSCLC after four cycles of initial platinum doublet chemotherapy, in patients with non-SCC histology, “switch maintenance” chemotherapy with pemetrexed improves progression free survival and overall survival. Last reviewed December 2015	II	[6]
In patients with stable or responsive advanced NSCLC after four cycles of initial platinum doublet chemotherapy, “switch maintenance” therapy with erlotinib improves progression free survival and overall survival. Last reviewed December 2015	II	[6]

Evidence-based recommendation	Grade
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.	**A**

Evidence-based recommendation	Grade
Options for delaying tumour progression in unselected patients, include erlotinib or docetaxel, whilst in patients with non-squamous cell carcinoma histology, pemetrexed or erlotinib. Options most proven for prolongation of survival include erlotinib or pemetrexed. In the case of patients with known EGFR-gene activating mutations treated initially with chemotherapy, switch maintenance erlotinib is recommended. Last reviewed December 2015	

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2.45 Optimal second-line therapy

Contents

2.45.1 What is the optimal second-line therapy in patients with stage IV inoperable NSCLC?

2.45.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.45.1.1.1 Monotherapy in unselected patients

Several randomised controlled trials (RCTs) have been reported examining the role of second line systemic therapy in unselected patients. The first studies examined docetaxel, establishing it as a standard of care in suitably fit patients. Subsequent studies examined different schedules of docetaxel, or examined the efficacy of new agents using it as the reference standard.

In 2000, two key RCTs were reported evaluating the efficacy of single agent docetaxel in previously treated NSCLC. Shepherd et al evaluated the efficacy of docetaxel versus best supportive care in 104 patients previously treated with platinum-based chemotherapy.[1] Compared with best supportive care, docetaxel 75 mg /m2 Q three-weekly, improved one-year survival (37% versus 11%; P = 0 .003).[1] Fossella et al randomised 373 previously treated patients with advanced NSCLC to two dose regimens of docetaxel compared with control arm of vinorelbine or ifosfamide.[2] one-year survival was significantly greater with docetaxel 75 mg/m2 than with the control treatment (32% versus 19%; P = 0.025,). Based on these two studies, docetaxel became the standard of care as second-line treatment of advanced NSCLC. Further supporting the clinical value of docetaxel was the results of the QOL analysis in the Shepherd study, which indicated less deterioration in QOL for docetaxel treated patients compared with best supportive care.[3]

Bria et al, compared the efficacy of weekly docetaxel with the reference standard of three-weekly, by evaluating data from 1018 patients from six RCTs. No significant differences in OS or RR in favour of the weekly schedule were found, however weekly docetaxel was associated with fewer grade ¾ neutropaenic events.[4]

Hanna et al, then compared single agent pemetrexed to three-weekly docetaxel as second line monotherapy of advanced NSCLC.[5] This study of 571 patients, randomised to three-weekly pemetrexed or docetaxel, showed equivalent efficacy outcomes (PFS, one-year survival) but significantly fewer side effects in favour of pemetrexed.[5] Consequently, pemetrexed was soon registered as an alternative second-line agent in NSCLC. Scagliotti et al in a post hoc analysis of data from two RCTS of pemetrexed, subsequently showed that pemetrexed increased OS in patients with non-SCC histology (p = 0.047), whereas OS was decreased with pemetrexed in SCC histology (p = 0.018).[6] A subsequent systematic review has confirmed this treatment-by-histology interaction effect with pemetrexed treatment showing greatest benefit in non-SCC histology.[7]

Two studies evaluated the effectiveness of the single agent first generation EGFR TKIs gefitinib or erlotinib compared with placebo in previously treated patients with NSCLC.[8][9] Thatcher et al, reported the effect of gefitinib as second or third-line therapy in 1692 patients with NSCLC refractory to or intolerant of previous treatment (ISEL study). Median survival was not significantly different between gefitinib and placebo treated patients in the overall population or the pre-specified adenocarcinoma subgroup.[8] However, in pre-planned subgroup analyses, OS was longer with gefitinib in never-smokers (n = 375, OS HR 0.67 (95% CI 0.49-0.92), p = 0.012) and patients of Asian origin (n = 342, OS HR 0.66 (95% CI 0.48-0.91)).[8] This sub-group effect most likely can be attributed to the greater incidence of activating EGFR gene mutations in this population.

Shepherd et al, randomised 731 patients, previously treated for advanced NSCLC, to receive erlotinib 150 mg daily or placebo as second or third-line treatment (BR21 study). A RR of 8.9 % was observed with erlotinib, which was shown to prolong OS (median 6.7 months (erlotinib) versus 4.7 months (placebo); HR 0.70, p <0.001).[9] More patients receiving erlotinib had improvements in cough, pain, dyspnoea and in the overall physical function domain of QOL.[9]

Kim et al randomised 1433 patients previously treated for advanced NSCLC to receive gefitinib 250 mg daily or three-weekly docetaxel chemotherapy (INTEREST study).[10] The primary objective was to compare OS and to assess non-inferiority of gefitinib in the overall population and superiority in patients with high EGFR gene copy number.[10] Non- inferiority of gefitinib compared with docetaxel was confirmed for OS (HR 1.02, 95% CI 0.905 – 1.15). Superiority of gefitinib in patients with high EGFR gene copy number was not proven. Skin rash and diarrhea were more common with gefitinib, whilst neutropaenia, asthenia and alopecia were more common with docetaxel.[10]

Ciuleanu et al, randomised patients that progressed after first line platinum doublet chemotherapy to recive either erlotinib 150 mg daily or chemotherapy (pemetrexed or docetaxel by investigator choice). This study (TITAN) was originally designed to test for superiority of erlotinib versus chemotherapy, in patients progressing after the induction chemotherapy phase of the switch maintenance erlotinib study by Capuzzo et al.[11][12] However, when the Capuzzo study closed, so to did recruitment to the TITAN study. Nonetheless, for the 424 patients randomised, median overall survival was 5.3 months (95% CI 4.0–6.0) with erlotinib and 5.5 months (4.4–7.1) with chemotherapy (HR 0.96, 95% CI 0.78–1.19; log-rank p=0.73). The adverse-event profile of each group was in line with previous studies, with more skin rash and diarrhea with erlotinib, and alopecia associated with chemotherapy (mainly due to docetaxel).[12]

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2.45.1.1.2 Combination therapy in unselected patients

Di Maio et al, examined whether doublet chemotherapy is more effective than single agent chemotherapy as second-line treatment of advanced NSCLC in 847 patients from six RCTS from 1999 – 2005.[13] Single agents evaluated include docetaxel (three studies), irinotecan, cisplatin, or pemetrexed. Response rate was greater for doublet therapy (15 % versus 7.3 %, p = 0.0004), as was PFS (HR 0.79, 95% CI 0.68 – 0.91).[13] However, there was no significant difference in OS between single agent and doublet chemotherapy and there were significantly more grade ¾ haematologic and non-haematologic toxicities with doublet chemotherapy.[13]

Qi et al, examined whether doublet pemetrexed based therapy is more effective than single agent pemetrexed as second-line treatment of advanced NSCLC in 1,186 patients from five RCTS from 1999 – 2005.[14] Only one of these studies was a phase III RCT, that of the dual targeted TKI vandetanib (anti-VEGF and anti EGFR).[15] Here doublet therapy was associated with a greater RR, but did not improve PFS).[15] The other four phase II RCTS evaluated the addition of carboplatin, and the new agents enzastorurin, matuzumab and bortezomib to pemetrexed.[14] Overall, there was improvement in RR and PFS with doublet therapy but not survival.[14] Furthermore, there was more grade ¾ neutropaenia and thrombocytopaenia with the doublet therapy.[14]

Herbst et al, also evaluated the efficacy of vandetanib. In their double blind RCT, the effect of Vandetanib plus docetaxel was compared with docetaxel as second-line treatment for patients with advanced NSCLC, on PFS in 1391 patients.[16] Vandetanib plus docetaxel was shown to be an active regimen with significant improvement in PFS versus placebo plus docetaxel (HR 0.79, 97.58% CI 0.70–0.90; p<0.0001).[16], however, the size of the effect on median PFS was small (4.0 months (vandetanib) versus 3.2 months (placebo), and therefore of questionable clinical significance, and survival benefit not shown.[16]

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2.45.2 Evidence summary and recommendations

Evidence summary	Level	References
In previously treated patients with advanced NSCLC, single agent docetaxel 75 mg /m2 improves survival compared with best supportive care or vinorelbine and ifosfamide. Last reviewed December 2015	II	[1], [2]
In previously treated patients with advanced NSCLC, single agent pemetrexed has similar efficacy but fewer side effects than three-weekly docetaxel. Last reviewed December 2015	II	[5]
In previously treated patients with advanced NSCLC, compared with docetaxel, pemetrexed appears to have greater efficacy in non-squamous cell carcinoma histology, and inferior efficacy in squamous cell carcinoma. Last reviewed December 2015	I	[7]

Evidence-based recommendation	Grade
	B

Evidence-based recommendation	Grade
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. Last reviewed December 2015	

Evidence summary	Level	References
In unselected previously treated patients with advanced NSCLC single agent erlotinib150 mg per day orally as second-line therapy improves survival compared with placebo. Last reviewed December 2015	II	[9]
In unselected previously treated patients with advanced NSCLC, single agent gefitinib 250 mg per day orally does not improve survival compared with placebo. Last reviewed December 2015	II	[8]
In unselected previously treated patients with advanced NSCLC, gefitinib 250 mg per day orally is equivalent to three-weekly docetaxel chemotherapy. Last reviewed December 2015	II	[10]
In unselected patients with advanced NSCLC, progressing after first-line platinum-based chemotherapy, there is no difference in survival between erlotinib 150 mg daily or chemotherapy (either pemetrexed or docetaxel). Last reviewed December 2015	II	[12]

Evidence-based recommendation	Grade
In unselected patients previously treated for advanced NSCLC, erlotinib 150 mg per day orally can be used as second-line therapy, instead of chemotherapy. Last reviewed December 2015	**B**

Evidence summary	Level	References
Doublet therapy as second-line treatment of advanced NSCLC increases response rate and progression free survival, but is more toxic and does not improve overall survival compared with single agent chemotherapy. Last reviewed December 2015	I	[13], [14]

Evidence-based recommendation	Grade
Doublet therapy is not recommended as second-line treatment of advanced NSCLC . Last reviewed December 2015	**A**

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2.46 Optimal third-line therapy in unselected patients

Contents

2.46.1 What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC?

2.46.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of the following question is based on the evidence in support of the old and new practice paradigms for stage IV NSCLC. Empirical therapy refers to therapy given to all fit patients deemed suitable without any particular restrictions.

2.46.1.1.1 Third-line therapy

Few randomised controlled trials (RCTs) have evaluated third line therapy in unselected patients with advanced NSCLC. The aforementioned negative RCT (ISEL) of gefitinib versus placebo in 1692 patients included 847 patients (50%) that had received two previous lines of therapy.[1] The positive RCT (BR21) of erlotinib versus placebo in 731 patients included approximately 50% of patients having received two previous lines of therapy. Univariate analysis of OS by number of prior regimens found OS remained in favour of erlotinib (compared with placebo) by similar magnitude to the overall study population results (HR 0.80, p = 0.02).[2] The study by Kim et al, comparing gefitinib to docetaxel in previously treated advanced NSCLC, only included 235 (16%) patients that had received two previous lines of therapy. Analysis of OS number of prior regimens found OS more in favour of docetaxel. But as this is a post hoc analysis with small patient numbers, it is not appropriate to draw conclusions.[3]

2.46.2 Evidence summary and recommendations

Evidence summary	Level	References
In unselected previously treated patients with advanced NSCLC who have received two lines of therapy, single agent erlotinib 150 mg per day orally as third-line therapy improves survival compared with placebo. Last reviewed December 2015	II	[2]

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**B**

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2.47 Optimal systemic therapy regimen - poor performance status

Contents

2.47.1 What is the optimal systemic therapy regimen for patients with poor performance status for treatment of stage IV inoperable NSCLC?

2.47.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here The focus of this question is the evidence in support of the old practice paradigm for empirical chemotherapy for stage IV NSCLC. Empirical therapy here refers to therapy given to all patients with poor performance status.

2.47.1.1.1 Poor performance status patients

Most studies with cytotoxic chemotherapy have been evaluated in “fit” patients, predominantly with PS 0 or 1. Patients with PS 2 are generally considered a poor prognostic group and at higher risk of toxicity, particularly from cytotoxic chemotherapy. Attempts to improve outcomes in this poor performance group population (PS 2) of patients with advanced NSCLC have been challenging with trials focused on the use of less toxic regimes or monotherapy with 3G agents or anti-EGFR TKIs.

Liu et al undertook a systematic review of phase II and II studies to examine the safety and efficacy of EGFR TKI monotherapy versus single-agent chemotherapy using third-generation cytotoxics as first-line treatment for patients with advanced non-small cell lung cancer and poor performance status.[1] No randomised controlled trials (RCTs) were identified. Fifteen single arm phase II studies (1425 patients) were evaluated to determine pooled estimates for RR and safety. The pooled RR (95% CI) to EGFR TKIs for unselected populations was 6% (3–8%), which compares with 9% (6–13%) reported by single-agent 3G chemotherapy trials. By summary comparison only, toxicity profiles were more favourable for the EGFR TKIs than chemotherapy. This study confirms the feasibility of treatment in the poor PS population but does not provide information on the overall benefit of such treatment.

Baggstrom et al reported a meta-analysis of five trials (n =1029 patients) compared 3G single agents with BSC. Four of the trials included a BSC control arm, and one trial included 5-fluorouracil (5FU)/ leucovorin as the control arm.[2] Response rates for the 3G agents ranged from 12% to 20%. One-year survival favored the 3G agents over BSC with risk difference of 7% (95% CI: 2% to 12%).[2] The number needed to treat for one patient to realise a benefit in the probability of one-year survival was 14.[2] These five trials evaluated single agent vinorelbine, paclitaxel, docetaxel and gemcitabine.[3][4][5][6][7] The study by Crawford et al of single agent vinorelbine included 50% of patients with low PS, the vinoerlbine study by Gridelli et al in patients over 70 included 24% of patients with PS 2, the paclitaxel study by Ranson et al included 15% PS 2 patients, the docetaxel study by Roszkowski et al, included 20% PS 2 patients whilst the gemcitabine study by Anderson et al was mainly in low PS patients.[3][4][5][6][7] The study by Anderson et al of gemcitabine versus best supportive care evaluated QOL as its primary endpoint and confirmed better QOL and reduced disease-related symptoms compared with those receiving best supportive care alone, although breathlessness was least well palliated and OS was no different.[5] Quality of life was also in favour of paclitaxel, docetaxel and vinorelbine (versus best supportive care) in the respective studies.[4][6][7]

In the second-line setting, several of the key RCTs that evaluated the efficacy of EGFR TKIs have included PS 2 or greater patients.[8][9][10] Both the placebo controlled trials of gefitinib and erlotinib enrolled > 30 % of patients with PS 2, whilst the study by Kim et al comparing gefitinib to docetaxel included 11% of PS 2 patients. In the BR21 study, analysis of benefit by the PS 2 and 3 subgroups that received erlotinib versus placebo demonstrated a benefit in OS (HR 0.8; 95% CI 05-1.1 (PS 2); 0.4-1.3 (PS 3)), which compares with OS HR 0.7 for the overall population. (0.6-0.9).[8] Thatcher et al, demonstrated the direction of benefit to be in favour of gefitinib over placebo in the OS analysis by sub-populations (30% of patients with PS2).[9]. In the small PS2 sub-population in the study by Kim et al comparing gefitinib with docetaxel, the direction of benefit favoured gefitinib but the confidence limits were wide.[10] Overall. confident conclusions cannot be made for benefit from gefitinib in unselected PS 2 or more patients. However, given the magnitude of benefit observed with gefitinib in first line patients with activating EGFR gene mutations (GMT+, ,described in the section below)[11], it would be reasonable to expect that EGFR GMT + "selected" patients may still potentially benefit from an EGFR TKI , even if of poor performance status, given the size of the observed benefit and relatively low toxicity.

2.47.2 Evidence summary and recommendations

Evidence summary	Level	References
In patients with poor performance status (PS 2), first-line monotherapy with 3G chemotherapy (vinorelbine, gemcitabine, paclitaxel or docetaxel) may improve survival and/or quality of life. Last reviewed December 2015	I, II	[3], [4], [5], [6], [7], [2]

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**B**

Evidence summary	Level	References
There is evidence for benefit with erlotinib 150 mg daily as second or third-line therapy in unselected poor performance status patients (PS2 or 3) . Last reviewed December 2015	II	[8]

Evidence-based recommendation	Grade
Poor performance status patients having received 1 or 2 lines of prior therapy, may be offered erlotinib 150 mg daily. Last reviewed December 2015	**B**

Practice point
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. Last reviewed December 2015

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2.48 Optimal systemic therapy regimen for elderly patients

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2.48.1 What is the optimal systemic therapy regimen for elderly patients for treatment of stage IV inoperable NSCLC?

2.48.1.1 Introduction

The majority of patients treated with systemic therapy for NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of this question is the evidence in support of the old practice paradigm for empirical chemotherapy for stage IV NSCLC. Empirical therapy here refers to therapy given to all elderly patients as defined below.

2.48.1.1.1 Systemic therapy for elderly patients

The age criterion for designation of “elderly” has varied somewhat across NSCLC studies with the elderly groups commonly defined as those patients either 65 or 70 years of age or older. Several randomised controlled trials (RCTs) have been conducted within this subgroup. As a group elderly patients are considered at higher risk of treatment related toxicity, due to possible age physiologic effects on drug handling and high proportion of co-morbidities. Gridelli et al first reported findings to indicate benefit from monotherapy with vinorelbine in patients over 70, with improvement seen in OS 0.65 (95% CI = 0.45–0.93) and fewer reported lung cancer related symptoms in a RCT of 161 patients[1] Kudoh et al, subsequently compared docetaxel 60 mg/m2 (day one) to vinorelbine 25 mg/m2 (days one and eight) every 21 days for four cycles, in a RCT of 182 Japanese patients over 70 years of age.[2] There was no statistical difference in the primary endpoint of median OS with docetaxel versus vinorelbine (14.3 months versus 9.9 months; HR 0.780; 95% CI 0.561 - 1.085; P = 0.138).[2] However, median PFS (5.5 months versus 3.1 months; P = 0.001), RR (22.7% versus 9.9%; P = 0.019) and disease-related symptoms favoured docetaxel over vinorelbine (odds ratio, 1.86; 95% CI, 1.09 - 3.20). Docetaxel was associated with more grade 3/4 neutropaenia (82.9% for docetaxel; 69.2% for vinorelbine; P = 0.031).[2]

Hainsworth et al, randomised 350 patients over 65 years of age to first line single-agent weekly docetaxel versus the combination of docetaxel and gemcitabine.[3] There was no difference in OS with the combination treatment compared with single agent weekly docetaxel.[3] Russo et al reported a literature-based meta-analysis of RCTs that compared a gemcitabine based doublet regimen with a 3G single agent in elderly patients (> 65).[4] This meta-analysis included the study by Hainsworth et al. Four trials evaluating 1436 patients were included in the meta-analysis. A significant difference in RR was seen favouring gemcitabine doublet therapy over single 3G agents (OR 0.65; 95% CI 0.51-0.82, p < .001), whereas one-year survival rate was not significantly different (OR, 0.78; 95% CI, 0.57-1.06, P = 0.169). Only Grade ¾ thrombocytopaenia was greater with combination therapy (OR, 1.76; 95% CI, 1.12-2.76, P= 0.014).

More recently, Quoix et al reported findings from a RCT of that compared a carboplatin and paclitaxel doublet chemotherapy regimen with 3G monotherapy in 451 elderly patients (age 70-89) with advanced NSCLC.[5] Patients were treated with carboplatin AUC 6 on day one and 90 mg/m. paclitaxel on days 1, 8, and 15 Q4 weekly or 3G monotherapy with either 25 mg/m2. vinorelbine on days one and eight or 1150 mg/m2 gemcitabine on days one and eight, Q3 weekly.[5] Overall survival was in favour of the combination (median 10.3 months for doublet chemotherapy versus 6.2 months for 3G monotherapy (HR 0.64, 95% CI 0.52–0.78; p<0.0001)).[5] Toxicity was more frequent in the doublet chemotherapy group than in the monotherapy group (neutropaenia (48.4% vs 12.4%); asthenia (10.3% versus 5.8%)[5]

2.48.2 Evidence summary and recommendations

Evidence summary	Level	References
First-line single agent vinorelbine (30 mg/m2 on days one and eight, Q3 weekly) in patients over 70 years of age improves survival and reduces disease related symptoms. Last reviewed December 2015	II	[1]
In patients over 70 years of age, first line single agent docetaxel 60 mg/m2 (day one) compared to vinorelbine 25 mg/m2 (days one and eight) every 21 days, improves response rate, progression free survival and disease related symptoms, but not overall survival and is associated with more G3/4 neutropaenia. Last reviewed December 2015	II	[2]
In patients over 65 years of age, gemcitabine doublet chemotherapy improves response rate compared with single agent 3G chemotherapy, but does not improve survival and is associated with greater thrombocytopaenia. Last reviewed December 2015	I	[4]
In patients over 70 years of age, first-line carboplatin/weekly paclitaxel combination improves survival compared with 3G monotherapy (weekly vinorelbine or gemcitabine) but, is associated with more neutropaenia. Last reviewed December 2015	II	[5]

Evidence-based recommendation	Grade
	B

Evidence-based recommendation	Grade
Suitably fit patients over 65 years of age, can be offered first-line mono-chemotherapy with a 3G single agent (vinorelbine (25-30 mg/ m2 day one, eight Q3 weekly), docetaxel (60 mg/m2 day one, Q3 weekly) or gemcitabine (1150 mg/m2 days one and eight, Q3 weekly). Last reviewed December 2015	

Evidence-based recommendation	Grade
In elderly patients, first-line gemcitabine doublet chemotherapy is not recommended. Last reviewed December 2015	**B**

Evidence-based recommendation	Grade
In fit elderly patients, first-line carboplatin/weekly paclitaxel may be offered instead of 3G monotherapy, but at the expense of greater neutropaenia. Last reviewed December 2015	**B**

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2.49 Optimal systemic therapy regimen in selected patients

Contents

2.49.1 What is the optimal systemic therapy regimen in selected patients for treatment of stage IV inoperable NSCLC?

2.49.1.1 Introduction

The majority of patients treated with NSCLC have stage IV disease, with common sites of metastases including lymph nodes, the pleura, liver, adrenal glands, bone and brain. Consequently, systemic therapy has been the mainstay of treatment attempting to control overall disease. A historical summary of the evolution of systemic drug treatment for stage IV NSCLC can be found here. The focus of this section of this guideline is based on the evidence in support of the new practice paradigm of treatment for stage IV NSCLC by selection, either by histology, clinical (patient) phenotype or by molecular tumour target.

2.49.1.1.1 Selection by histology

Stanfield et al conducted a systematic review of prospective, randomised controlled trials (RCTs) to examine whether histology had a treatment modifying effect (TME) on the efficacy outcomes (OS and PFS) of chemotherapeutic agents in patients with advanced NSCLC.[1] A total of 17 systematic reviews, five individual patient data (IPD) meta-analyses, and 165 potentially relevant primary studies were identified for full review.[1] Four of the five IPD meta-analyses investigated TME of histology and one did not, but none found a significant TME by histology. One hundred and twenty two (74%) of the 165 primary publications retrieved for full review did not report data in a way in which the TME of histology could be determined.[1] Data from three pemetrexed RCTs,comparing (i) second-line pemetrexed versus docetaxel, (ii) first-line pemetrexed and cisplatin versus gemcitabine and cisplatin, and (iii) switch maintenance pemetrexed versus placebo, showed a statistically significant TME by histology for OS and PFS.[1]

A fourth RCT comparing pemetrexed and carboplatin versus gemcitabine and carboplatin found no significant association between histology and OS.[1][2] Patients with non-SCC appear to gain the greatest benefit from treatment with pemetrexed, whilst patients with SCC appear to have poorer OS when pemetrexed is compared with other active treatments, and similar OS when compared with placebo.[1] A reproducible pattern of TME effect by histology was not seen clearly with other chemotherapeutic agents.[1]

Histology has also been shown to be a predictor for toxicity with the anti-VEGF Mab, bevacizumab, with higher incidence of pulmonary haemorrhage observed in SCC. Is histology also associated with a treatment modifying effect with bevacizumab? Sandler et al, in a post hoc analysis of their pivotal phase III RCT of first-line carboplatin/paclitaxel (PC) +/- bevacizumab (PCB) study in 878 carefully selected patients with non-SCC,

reported their findings by histologic subgroups.[3] The largest histologic subgroup in the study was adenocarcinoma (68.8% of patients), whilst not-otherwise specified represented 18.9% of patients. For adenocarcinoma, median OS was 10.3 months for PC treatment (n= 302) and 14.2 months for PCB (n = 300), HR 0.69 (95%CI: 0.58–0.83).[3] Sample sizes for other specific histologic subtypes were considered too small for meaningful comparisons.

The TME of histology in predicting benefit from pemetrexed, the observation of greater toxicity with bevacizumab and possibly other anti-VEGF therapies in SCC, and the finding of activating EGFR gene mutations (EGFR GMTs and other mutations) in adenocarcinomas has led to a great clinical need for diagnostic accuracy in the sub-classification of NSCLC on diagnostic specimens. Consequently, the International Association for the Study of Lung Cancer (IASLC) undertook a systematic literature review of the adenocarcinoma histologic classification.[4] In their review, Travis et al describe a revised classification system for diagnosing and reporting NSCLC with guidance for small biopsies, cytology and resected specimens, to enable classifying NSCLC primarily into adenocarcinoma or SCC due to the therapeutic implications of this distinction.[4]

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2.49.1.1.2 Selection by clinical phenotype

The early single arm and RCTs evaluating the first generation EGFR TKIs gefitinib and erlotinib identified that benefit from EGFR TKIs appeared to be greatest in certain NSCLC patient sub-populations: never smokers with adenocarcinoma, and especially, but not exclusively, in women,and Asian background.

Consequently, Mok et al, undertook a first-line RCT to compare gefitinib versus carboplatin/paclitaxel chemotherapy. They randomly assigned previously untreated patientsin East Asia who had advanced pulmonary adenocarcinoma and who were nonsmokers or former light smokers to receive gefitinib (250 mg per day) or carboplatin/paclitaxel chemotherapy.[5] The study met its primary objective of showing noninferiority of gefitinib and also showed its superiority, as compared with carboplatin– paclitaxel, with respect to PFS (HR 0.74; 95% CI 0.65 - 0.85; P<0.001). In the subgroup of 261 patients who were EGFR GMT + PFS was significantly longer with gefitinib than chemotherapy (HR 0.48; 95% CI 0.36 - 0.64; P<0.001), whereas in the subgroup of 176 patients who were negative for EGFR GMT, PFS was significantly longer among those who received chemotherapy than gefitinib (HR for progression or death with gefitinib 2.85; 95% CI,2.05 - 3.98; P<0.001). The most common adverse events in the gefitinib group were rash or acne (in 66.2% of patients) and diarrhea (46.6%).

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2.49.1.1.3 Selection by molecular testing of tumours

Several randomised controlled trials have been published with the first generation EGFR TKIs (gefitinib and erlotinib) in patients selected for treatment by the presence of an activating EGFR gene mutation.[6][7][8] All have compared first-line treatment with an EGFR TKI with standard chemotherapy on PFS. Similarly designed trials are in progress with newer generation EGFR targeting agents and inhibitors to other known driving molecular changes (eg. EML4-Alk gene fusion).

It is worth noting that this section on the evidence for treatment efficacy by molecular selection assumes that a validated method of molecular testing has been used, according to current best practice. It is acknowledged that more modern methods of gene sequencing/molecular profiling are likely to confer greater accuracy than early methods, some of which may have been used in these first generation clinical trials. A comprehensive review of the accuracy of the molecular methods used for the identification of EGFR gene mutation is being the scope of this guideline at this stage.

Bria et al has reported a literature-based meta-analysis undertaken to quantify the magnitude of benefit with upfront EGFR TKI in Asian patients with activating EGFR mutation (exon-19 deletions or exon-21 point mutations, (EGFR-GMT+)[9] They report findings from five RCTs involving 805 Asian patients, with results for efficacy in patients with activating EGFR mutations reported prospectively (three RCTS) or retrospectively (two RCTs).[9] Four trials evaluated the efficacy of gefitinib and one trial erlotinib, compared with a standard platinum based 3G chemotherapy regimen. EGFR TKI therapy significantly increased PFS (HR) 0.45, 95% CI: 0.36–0.58, P < 0.0001),and overall RR (HR 2.08, 95% CI 1.75–2.46, P < 0.0001) over chemotherapy, with significantly lower neutropaenia.[9] The absolute difference in PFS was 26%, corresponding to three to four patients needed to treat for one to benefit, whilst the absolute difference in RR was 36.5%, which translating into two to three patients needed to treat for one to benefit.[9] No significant difference was observed in overall survival, thought largely to be due to treatment crossover with most patients initially treated with chemotherapy going on to receive EGFR TKIs at progression. The rate of exon-19 mutations, female gender, and nonsmoking status were identified as additional predictors of outcome in a meta-regression analysis.[9]

In a Caucasan population, Rosell et al, randomised 174 patients with advanced NSCLC and EGFR mutations (exon 19 deletion or L858R mutation in exon 21) to receive either first-line erlotinib 150 mg daily or a choice of a platinum based 3G doublet regimen. (cisplatin and gemcitabine or docetaxel).[10] The study met its primary endpoint of improved PFS at its pre-planned interim analysis, with median PFS in the erlotinib group of 9.7 months (95% CI 8.4−12.3), compared with 5.2 months (95% CI 4.5−5.8) in the standard chemotherapy group (HR 0.37, 95% CI 0.25−0.54; p<0.0001).[10] Response rate was also in favour of erlotinib (58% versus 15%).

These studies evaluating first line EGFR TKIs in EGFR GMT + patients, which demonstrate dramatic improvements in RR and PFS but not OS, have added to the debate regarding whether OS should remain the the most important therapeutic objective of first line studies in advanced NSCLC. As this guideline has demonstrated, there is evidence for improvement in PFS and OS beyond first line therapy with the use of first line maintenance, second line and even third line therapy. Survival post progression (SPP) on first line therapies has been evaluated in a systematic review by Hotta et al who reviewed 70 phase III trials initiated between 1988 and 2007 involving 38,721 patients with advanced NSCLC[11].

This review also included studies evaluating molecularly targeted agents but did not report results according to each agent nor whether these studies were only conducted inpatients with an identified molecular target. Nonetheless, Hotta et al observed a stronger association between median survival time (MST) and SPP (r^2 = 0.8917) than MST and median PFS time (r^2 = 0.2563), finding that SPP and MPFS can account for 89% and 25% of the variation in MST, respectively[11]. This association between MST and SPP became closer over the years from 1988 to 2007, leading to the conclusion that a PFS advantage from first line treatment is unlikely to be associated with an OS advantage due to this increasing impact of SPP on OS, and that prolongation of SPP might impact on the ability for OS to assessing true efficacy from early-line chemotherapy in future clinical trials[11]. In

simple terms, this review highlights the impact of cross over at the completion of initial study treatment to other active drug therapy. How does this relate to anti-EGFR TKIs? Assuming a majority of patients commenced in initial chemotherapy do get to cross over to anti-EGFR TKIs at progression then OS does not appear to be compromised for the population, as found in the Bria and Rosell studies[9][10]. However for an individual patient there is the potential risk that second line treatment may not occur. The study by Fidias et al of immediate versus delayed docetaxel in non progressing patients after first - line platinum based chemotherapy, demonstrated an attrition rate of 37% i.e. 58 of 156 patients allocated to receive docetaxel at progression did not end up getting treated, 43% (25/58) due to progressive disease [12]. Whilst this may not be the case for the less toxic EGFR TKIs, it would be unreasonable for any patient to miss out on receiving treatment that can result in such a large effect on RR and PFS.

2.49.2 Evidence summary and recommendations

Evidence summary	Level	References
Histology (non-squamous cell carcinoma versus squamous cell carcinoma) is associated with a significant treatment modifying effect for patients treated with pemetrexed based chemotherapy, with superior survival effect of pemetrexed observed in non-squamous cell carcinoma histology and inferior survival effect observed in squamous cell carcinoma histology, compared with other standard regimens when pemetrexed is used first-line, as switch maintenance or as second-line treatment. Last reviewed December 2015	I	[1]

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**A**

Practice point
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.

Practice point
A multidisciplinary team discussion may be required in order to decide on the most appropriate diagnostic method to obtain adequate tissue. Last reviewed December 2015

Evidence summary	Level	References
In Asian patients with advanced NSCLC and known common activating EGFR GMs (exon-19 deletions or exon-21 point mutations), first-line therapy with a first generation EGFR TKI (gefitinib or erlotinib) significantly prolongs progression free survival and increases overall response rate, compared with standard platinum-based chemotherapy. Last reviewed December 2015	I	[9]
In regards to progression free survival, first-line gefitinib is not inferior to carboplatin /paclitaxel chemotherapy in Asian patients, particularly females, with adenocarcinoma, who have never smoked. Last reviewed December 2015	II	[5]
In caucasian patients with advanced NSCLC and known activating EGFR GMs (exon-19 deletions or exon-21 point mutations), first-line therapy with erlotinib significantly prolongs progression free survival and increases overall response rate, compared with standard platinum based chemotherapy. Last reviewed December 2015	II	[10]

Evidence-based recommendation	Grade
Patients with known activating gene mutations (exon-19 deletions or exon-21 point mutations) to EGFR should be treated with an EGFR TKI. Last reviewed December 2015	**A**

Evidence summary	Level	References
Progression free survival is significantly longer among patients treated with initial chemotherapy, than those treated with gefitinib in patients known not to have EGFR mutations. Last reviewed December 2015	II	[5]

Evidence-based recommendation	Grade
Where EGFR mutation status is negative or unknown, patients should be treated with standard chemotherapy. Last reviewed December 2015	**B**

Practice point

The evidence in support of large treatment benefits with first-line EGFR TKIs in response rate and progression free survival 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 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.

Last reviewed December 2015

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2.49.3 References

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2.50 Optimal systemic therapy and duration

Contents

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.[1][2]

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[3][4][5] and meta-analyses.[6]

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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 Last reviewed November 2015	I	[1], [2]
Maintenance or consolidation therapy post response to initial beyond four cycles of chemotherapy. Last reviewed November 2015	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. Last reviewed November 2015	**B**

Evidence-based recommendation	Grade
Therapy beyond the standard four cycles of induction chemotherapy cannot be recommended. Last reviewed November 2015	**A**

Practice point

It is advisable to use platinum plus etoposide for four cycles in patients with limited stage small cell lung cancer. Last reviewed November 2015

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2.51 Optimal concurrent chemotherapy

Contents

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.[1] No advantage of irinotecan plus cisplatin versus cisplatin and etoposide in patients receiving concurrent accelerated hyperfractionated thoracic radiotherapy.[2]

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.[3][4] 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.[5]

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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. Last reviewed August 2015	II, IV	[1], [3], [4]
No advantage of irinotecan plus cisplatin versus cisplatin and etoposide in patients receiving concurrent accelerated hyperfractionated thoracic radiotherapy. Last reviewed August 2015	II	[2]

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. Last reviewed August 2015	**B**

Practice point

It is advisable to use three-weekly platinum and etoposide chemotherapy during concurrent chemoradiotherapy for limited stage small cell lung cancer.

Chest irradiation is optimally commenced early during the course of chemotherapy.

Last reviewed August 2015

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2.51.3 References

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2.52 Optimal dose and fractionation schedule of prophylactic cranial irradiation

Contents

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.[1]

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.[2] 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.[3] 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.[4] In this larger analysis, there were no differences in QOL or neurotoxicity observed between the different dose arms.

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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. Last reviewed December 2015	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. Last reviewed December 2015	**B**

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2.52.3 References

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2.53 Optimal treatment volume for thoracic radiotherapy?

Contents

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.[1][2] 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.

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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.[3] 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.[4] 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.[5] 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.

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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.[4][6][7][8][9][10][11][12][13] With the exception of one study[8] 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.

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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. Last reviewed December 2015	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. Last reviewed December 2015	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. Last reviewed December 2015	**B**

Evidence-based recommendation	Grade
Elective nodal irradiation may be omitted to reduce toxicity. Last reviewed December 2015	**C**

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.

Last reviewed December 2015

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2.53.3 References

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2.54 Optimal 1st line chemotherapy regimen and duration

Contents

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;[1] [2] and phase III trials;[3][4][5][6][7] platinum etopside combination is still considered as the gold standard.[8]

Based on phase III trials[9][10][11][12] and subsequent meta-analyses[13][14] 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-Caucasion population.[2]

The utility of triplet combinations have provided no additional benefit based on phase II trials[15][16]

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. Sunitinib may provide benefit when assessed in phase II trial.[17]

This conclusion is based upon phase II,[18] and randomised phase III trials.[19][20]

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2.54.2 Evidence summary and recommendations

Evidence summary	Level	References
	II	[1], [3], [4], [5]

Evidence summary	Level	References
The platinum etoposide combination is still considered as the standard first-line regimen. Last reviewed December 2015		[6]
Irinotecan combined with platinum may be as efficacious as platinum etoposide in specific populations but with differing toxicity profiles. Last reviewed December 2015	I, II	[13], [14], [9], [10], [11], [12]
The utility of triplet combinations have provided no additional benefit. Last reviewed December 2015	II	[15], [16]
The use of maintenance or consolidation therapy after initial response to first-line therapy has not been shown to be of added benefit. Last reviewed December 2015	II	[18], [19], [20]

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. Last reviewed December 2015	**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 aditional benefit. Last reviewed December 2015

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2.55 Optimal second-line therapy

Contents

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

Based on meta-analyses[1][2] 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.[3][1]

Amrubicin in a phase II trial has demonstrated superior response rate to topotecan in chemotherapy sensitive patients with less severe neutropenia.[4] This was not borne out in a phase II trial.[5] Other agents including bortezomib,[6] histone deacetylase inhibitors,[7] and mTOR inhibitors,[8] evaluated in phase II trials have demonstrated no benefit.

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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. Last reviewed December 2015	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. Last reviewed December 2015	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). Last reviewed December 2015	**A**

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2.56 Optimal dose and fractionation of prophylactic cranial irradiation

Contents

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.[1] 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.[2] 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.

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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. Last reviewed November 2015	II	[2]
Over this dose range, higher radiotherapy doses confer no survival advantage over lower ones Last reviewed November 2015	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. Last reviewed November 2015	**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.

Last reviewed November 2015

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2.56.3 References

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2.57 Thoracic radiotherapy

Contents

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

Three 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.[1][2][3]

An international collaborative randomized control trial of 498 patients confirmed a survival benefit at 2 years from the addition of consolidative thoracic radiotherapy in patients attaining response to initial chemotherapy.[3] Patients were randomised to 30Gy in 10 fractions preferably commencing within 6 weeks of chemotherapy cessation and usually about 1 week after PCI, or to no further treatment. As might be expected, given that many patients had metastatic ED SCLC, the primary endpoint of overall survival at 1 year was not met; but planned secondary analyses of overall survival at 2 years (13% vs 3%), intra-thoracic control and progression free survival were all significantly improved with radiotherapy. This was achieved without any significant increase in toxicity. Patients in whom chemotherapy had induced a complete response in the chest appeared not to benefit from thoracic radiotherapy.[4]

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.[1] The addition of thoracic radiotherapy (54Gy in 36 BD fractions) resulted in a statistically significant survival advantage. Apart from radiotherapy-related oesophagitis in 27% of patients, no further significant radiotherapy toxicities were observed.

A metanalysis of the two randomised trials above confirmed a statistically significant survival advantage to thoracic RT in ED SCLC (random-effects model HR, 0.81; 95% CI, 0.69-0.95; P = .01).[5] While there were no differences in bronchopulmonary toxicity between irradiated and non-irradiated groups, grade 3 oesophageal toxicity was significantly higher in the irradiated group (6.6% vs 0%). However, this was almost exclusively found in patients receiving 54Gy in the Jeremic et al trial[1] as opposed to those who received 30Gy in the trial by Slotman et al[3] (27% vs 2%).

Yee at al.[2] 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 also being addressed through the RTOG 0937 trial.

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2.57.2 Evidence summary and recommendations

Evidence summary	Level	References
In ED SCLC patients responding to initial chemotherapy, moderate dose thoracic radiotherapy to 30Gy in 10 fractions improves overall survival at time points greater than 18 months with no severe acute or late toxic effects. Last reviewed December 2015	II	[3], [1]

Evidence-based recommendation	Grade
Strongly consider administering moderate dose consolidative chest radiotherapy (30 Gy in 10 fractions) to chemotherapy responders, especially those with residual disease in the thorax. Last reviewed December 2015	**B**

Practice point
Chest radiotherapy was administered 6-7 weeks after chemotherapy and usually 1 week after completion of prophylactic cranial irradiation.

Practice point

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.

Last reviewed December 2015

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2.57.3 References

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2.58 Palliative care in symptom management

Contents

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.[1] 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.[2]

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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.[3] 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.

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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.[4]

Morphine remains the recommended opioid based on familiarity, cost and ease of access.A systematic review of 54 randomised studies [5] 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 form 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 hydormorphone for acute and chronic pain[6] and nine randomised studies methadone for cancer pain. A meta-analysis of four RCT's[7] 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.[8] 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.[9] 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 bisphophonates for the relief of pain from bone metastasis.[10] 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[11] 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.[12][13][14] A systematic review of three RCT"s[12] 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.[14]

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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.[15] 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 [16] 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.[17]

Benzodiazepines are also commonly used in the management of breathlessness but a systematic review of seven studies showed no evidence for a beneficial effect.[18] 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.[15]

Data from a systematic review of non-pharmacological interventions for breathlessness from 47 studies.[19] 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 [20] 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.

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2.58.1.2.3 Constipation

Data form a systematic review[21] 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 form 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.

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2.58.1.2.4 Cough

A phase II study of hydrocodone[22] 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[23] examined the results of 17 RCT's. No practice recommendations were concluded due to the absence of credible evidence. No clear conclusions were possible form the use of pharmacological interventions though butamirate linctus, codeine (60mg), dihydrocodeine (10mg), cromoglycate and hydropropizine / levodroprozine 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.

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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.[24] A low incidence of side effects confirmed the relative safety of this drug.

Low level evidence suggests the potential usefulness of transcathether arterial embolisation (TAE)[25] or bronchial artery embolisation.[26] 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)*

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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. Last reviewed December 2015	I	[5]
Oxycodone, hydromorphone and methadone can provide comparable analgesia to morphine when titrated to effect. Last reviewed December 2015	I	[27], [28], [29]
	I	[30]

Evidence summary	Level	References
NSAIDS alone is superior to placebo and adequate for the management of mild cancer pain Last reviewed December 2015		
Bisphosphonates and radiopharmaceuticals should be considered where analgesics and /or radiotherapy are inadequate for the management of painful bone metastasis. Last reviewed December 2015	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. Last reviewed December 2015	**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. Last reviewed December 2015	**B**

Practice point

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

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. Last reviewed December 2015	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. Last reviewed December 2015	I	[16], [33], [15]

Evidence-based recommendation	Grade
The use of opioids are recommended for the relief of dyspnoea in patients with NSCLC. Last reviewed December 2015	**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. Last reviewed December 2015	**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. Last reviewed December 2015

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.

Last reviewed December 2015

Evidence summary	Level	References
The evidence suggests that opioid receptor antagonists such as methylnaltrexone, are effective in inducing laxation for opioid induced constipation. Last reviewed December 2015	I	[21]

Evidence-based recommendation	Grade
Subcutaneous methylnaltrexone should be considered in patients where conventional laxatives have failed. Last reviewed December 2015	**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.

Last reviewed December 2015

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 mucopurulant sputum.

Practice point

-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

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.
Last reviewed December 2015

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2.59 Advance care planning and referral

Contents

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 of this guideline 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 2014, it was the leading cause of cancer deaths in Australian men and women and was responsible for the deaths of 8,251 Australians, making it the fourth leading cause of death.[1] The prognosis after the diagnosis of stage IV (metastatic) lung cancer has been estimated to be less than one year.[2] 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.

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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[2] 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.[3]

In contrast a RCT conducted in Australia found a different result.[4] This study included patients who had a range of different advanced malignancies (including lung cancer) and compared the effect on QOL and mortality of early referral to a Palliative Care nurse to usual care.[4] In the early referral group, there was a trend toward decreased quality of life and a statistically significant decrease in mortality.[4] Patients in this study received a relatively ‘low dose’ of palliative care involvement compared with the study by Temel et al [2] quoted above. Additionally, despite randomisation, there were some important differences between the groups at baseline which may explain some of the results. The authors suggest that the change in QOL may partially be explained by patients in the intervention arm being more comfortable disclosing symptoms and/or those in the control arm maintaining denial as a coping mechanism for longer.

Overall, the preponderance of evidence remains in favour of early referral to palliative care, but other factors, including the ‘dose’ of palliative care may be important.

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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.[5] 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.[6] 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.[7]

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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.[5] 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.[8]

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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,[9] however, with respect to lung cancer, clinicians may not adequately communicate prognosis.[10] Patients with other solid malignancies tend to overestimate their prognosis, however this issue has not been addressed in patients with lung cancer.[11] 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.[12][13][14] Accurate prognostic understanding may be associated with a decreased desire for CPR and/or intensive care admission and an increased preference for hospice care.[15]

A minority of patients with advanced lung cancer have had discussions regarding resuscitation status with their clinicians.[16][17] 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,[18][13] and may rely on the responsible physician and/or the health care system to initiate such discussions.[19] When patients have not completed an advance care plan their next of kin may not fully understand their wishes.[13] In contrast,

when advance care directives have been completed, bereaved family members report it was helpful in guiding care prior to death.[20] 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.[21][22] 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.[2]

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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.[7] 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.[6] Importantly, patients and their families may not always recognise when the topic of end of life or advance care planning has been raised,[23] so it may be necessary to sensitively check the patients' and their families understanding the issue in subsequent conversations.

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.[9] They value compassion, care and empathy in the delivery of this type of information.[9] However, the information needs of patients and their care givers may vary over time, with care givers generally wanting more information as time proceeds {Cite footnote|Citation:Parker SM, Clayton JM, Hancock K, Walder S, Butow PN, Carrick S, et al 2007}} Patients may change their mind about how much information they want about their illness over time, with some wanting more and some wanting less information as their illness unfolds.[24] In addition, patients preferences regarding who should control decision making (ie doctor controlled, shared or patient controlled) may fluctuate over time.[24] These changes may be unpredictable and thus repeatedly exploring these preferences may be appropriate. [24][9]

Patients may need time to process the idea that end of life is approaching and doctors may delay discussions until there is definite evidence of medical deterioration, by which time, end of life may be quite close.[23] Furthermore, there are cultural factors which may impact on information needs and some patients with lung cancer experience stigma which complicate communication and information needs.[25]

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.[26] Some patients prefer to almost unilaterally make their own decisions while others prefer medical staff to have ultimate decision making authority.[26] 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.[27] Taken together, this evidence suggests the importance of exploring patient understanding and preferences as well as 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,[28] 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.[14] 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.[12] When decisions to limit life prolonging interventions are made, it is important to then emphasise that care will continue to be provided to ensure that the person is supported throughout the course of their illness.[29] As with all medical care, it is important to document the outcomes of these types of discussions.

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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, however the amount of contact from the palliative care service may be important. Last reviewed December 2015	II	[2], [4]

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. Last reviewed December 2015	**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. Last reviewed December 2015	II	[5]

Evidence-based recommendation	Grade
Advance care planning discussions should be initiated with patients, as there are multiple benefits. Last reviewed December 2015	**B**

Evidence summary	Level	References
The evidence suggests that there is a need for patient centred advance care planning to address the gaps between clinician and patient expectation and to better understand patients' preferences. Last reviewed December 2015	II, IV	[2], [16], [17], [18], [13], [20], [21], [22]

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. Last reviewed December 2015	**C**

Practice point
Consider referral to palliative care when metastatic disease is diagnosed. Don't wait until there is definite evidence of medical deterioration. Last reviewed December 2015

Practice point

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.

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2.59.3 References

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2.60 Psychological support and interventions

Contents

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,[1] with studies quoting up to 43% of lung cancer patients experiencing psychological distress compared with approximately 35% of patients with other cancer diagnoses.[2] The psychological distress of lung cancer patients has been found to persist throughout the clinical course of illness [3] as poor prognosis, symptom severity and treatment side-effects of lung cancer adversely affects psychological wellbeing.[4] 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.[5][6]

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.

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2.60.1.2 Psychosocial treatment of depression

There have been five recent systematic reviews[7][8][9][10][11] and one meta-analysis[12] evaluating the efficacy of psychological interventions for the treatment of depression in samples of mixed cancer patients.

Barsevic et al[7] 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[10] 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[8] and a meta-analysis by Osborne et al[12] suggested that that Cognitive Behaviour Therapy (CBT) was effective in the management of depression particularly in the short-term.

In a recent RCT utilizing a collaborative and integrated approach that involved a multidisciplinary team (e.g.: nursing, psychiatry, oncology) and a combination of CBT strategies (such as problem-solving, psychoeducation, and behavioural activation), rapport building, counselling techniques and anti-depressant medication, it was found that depression severity was significantly lower in patients allocated to the collaborative depression care group (mean score on the SCL-20 1.24 [SD 0.64]) than in those allocated to a treatment as usual group (mean score 1.61 [SD 0.58]); difference −0.38 (95% CI −0.58 to −0.18). These improvements were also maintained at 12 weeks.[13]

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.[8] 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.[9] 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.[12] 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[8],[9] involved either a mixed sample of cancer survivors or focused on patients with advanced cancer. All three reviews commented on inconsistencies in the methodoclogical quality of studies examined, whilst Newell et al provided a summary of quality indicators to ensure methodological rigour of future studies could be improved.[8]

In summary, "whilst it may be reasonable to treat depression in individuals with lung cancer with standard treatments until more specific evidence is available, clinicians should be aware that the effectiveness and potential adverse effects of these treatments remain unknown in this patient group."[11]

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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.[14]. Newell et al in a systematic review did not find consistent evidence for the use of CBT to treat anxiety,[8] 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).[12]

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.[10] 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.[15] Some evidence is also starting to emerge that individual narrative meaning making interventions (e.g: where patients are promoted to discuss their sense of ‘‘meaning’’, psychological, physical, social and spiritual wellbeing and sense of suffering) may have a role in improving anxiety and depression, however, larger powered trials are required to draw any conclusions.[16]

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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.[17][18][19]

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.[20] Of these latter studies, four studies indicated that 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.[20] Overall the Cochrane review concluded that evidence for fatigue management was weak to moderate with fatigue specific interventions having better outcomes.

Kangas et al[21] 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.[21] Similarly to the Cochrane review,[20] Kangas et al concluded that these studies, which specifically targeted fatigue in their hypothesis, yielded larger effect sizes.

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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).[22] 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.[23] An innovative intervention study,[23] conducted with 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.[24] In a more recent RCT, Carlson et al (2013)[25] found that pain was also significantly reduced in patients with lung cancer who received a thorough triage (e.g: Distress Thermometer, Canadian Problem Checklist (CPC), Pain Thermometer, Fatigue Thermometer, and the Psychological Screen plus the option of a phone call) versus minimal screening (e.g: Distress Thermometer).

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2.60.1.6 Quality of life

Uttierhoeve et al[10] 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[26] 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).[12]

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.[27] A recent study, however, found no evidence that a nurse navigation intervention was more effective in improving quality of life than treatment as usual.[28]

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2.60.1.7 Dyadic Interventions

There is a small body of research emerging that is examining the role that dyadic intervention may have in improving the psychosocial impacts of lung cancer. For instance, Badr, Smith, Goldstein, Gomez, Redd (2015)[29] conducted a pilot study examining the feasibility, acceptability, of a 6-session telephone-based dyadic psychosocial intervention. The intervention was grounded in Self-determination Theory and covered the following topics: self-care, stress and coping, symptom management, effective communication, problem-solving, and maintaining and enhancing relationships for both patients and carers. The intervention was found to led to significant improvements in depression, anxiety, and caregiver burden. Similarly Northouse, Mood Schafenacker, Kalemkerian , Zalupski, & LoRusso (2013)[30] found positive effects from that dyadic intervention. They found that dyadic interventions led to improvements in dyads' coping ($p<.05$), self-efficacy ($p<.05$), and social QOL ($p<.01$), and in caregivers' emotional QOL ($p<.05$). These studies although promising have a number of limitations including the involvement of a small number of lung cancer patients and inconsistent methodology and outcome measures. More RCTs are needed before we can conclude whether Dyadic interventions are beneficial for lung cancer patients.

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2.60.1.8 Conclusion

The diagnosis of stage IV NSCLC impacts on physical, psychological well-being and QoL of patients. The Psychosocial Guidelines for Adults with Cancer[6] 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.

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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). Last reviewed December 2015	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], [12]

Evidence summary	Level	References
Last reviewed December 2015		

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. Last reviewed December 2015	**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. Last reviewed December 2015	**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. Last reviewed December 2015	I, II	[12], [14], [31], [32]
Supportive and Meaning-based Group Psychotherapies have a positive impact on anxiety. Last reviewed December 2015	I, II	[10], [15]

Evidence-based recommendation	Grade
	B

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. Last reviewed December 2015	

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. Last reviewed December 2015	**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. Last reviewed December 2015	I, II	[17], [18], [20], [21], [19]

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. Further randomised controlled trials involving adequately powered studies and consistent methodology can be conducted to ascertain unmet needs in advanced cancer. Last reviewed December 2015	**C**

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. Last reviewed December 2015	I, II	[22], [23], [24]

Evidence-based recommendation	Grade
Psychological interventions have an important role in the management of cancer related pain. Last reviewed December 2015	**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. Last reviewed December 2015	I	[10], [12], [26], [27]
Non- invasive nurse-led programs aimed to target symptom management lead to improvement in wellbeing and quality of life. Last reviewed December 2015	I	[27]

Evidence-based recommendation	Grade
Quality of life of lung patients may improve with behavioural, cognitive or social cognitive therapies. Last reviewed December 2015	**C**

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. Last reviewed December 2015	**C**

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2.60.3 References

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2.61 Optimal management of malignant pleural effusions

Contents

2.61.1 What is the optimal management of malignant pleural effusions?

2.61.1.1 Introduction

Malignant pleural effusion (MPE) is a common problem for patients with metastatic cancer. Symptoms may include dyspnoea and cough. Effective palliation of symptoms with the least morbidity is the goal of management..[1] The mechanisms that underpin the breathlessness are not well defined but are likely to extend beyond the effect of lung compression/deflation. Imbalance between respiratory effort and diaphragm motion may contribute to the complex sensation that is breathlessness.[2][3] Therefore, symptomatic benefit from draining effusions with apparently minimal lung expansion can be seen.

Management options include recurrent needle drainage, drainage by long term catheter, pleurodesis via instilling of sclerosant either by bedside (blind or ultrasound guided) insertion of chest tube or at VATS, and pleurectomy by VATS or an open approach. In cases of incomplete re expansion, options include long term catheter drainage and pleurectomy / decortication by VATS or an open approach.

2.61.1.1.1 Prevention of fluid re-accumulation

Repeated simple aspiration 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. However, randomised comparisons of simple aspiration with other interventions are lacking. In patients with better performance status, repeated simple aspiration may lead to adhesion formation that can in the future make lung expansion and pleural adhesions more difficult or less effective. Insertion of an indwelling intercostal catheter alone, without any attempt at pleurodesis, is not recommended.[4] The success rate of pleurodesis 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. At a 3 month analysis, repeat aspirations are cheaper than tunnelled pleural catheters, followed by bedside pleurodesis and thoracoscopic pleurodesis. At 12 months, bedside pleurodesis is cheaper than tunnelled pleural catheter followed by thoracoscopic pleurodesis and repeated aspirations.[5]

2.61.1.1.2 Long-term tunnelled catheter

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.[6] 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.[7] Even in cases where re-expansion is not anticipated, there is a small but significant rate of spontaneous pleurodesis.[8][9][10] They can be used as a means to instil talc and achieve pleurodesis.[11] Advantages of this option include: insertion under local anaesthetic, early ambulation and short hospital stay. Disadvantages include: ongoing cost of drainage bottles (presently met most often by the patient) and the requirement of longterm foreign body protruding from the chest with respect to infectious risk and patient preference. Overall, cost effectiveness is greater in patients with shorter life expectancy,[12] but the cost transfer from hospital to individual patients is problematic.

Compared to bedside talc pleurodesis, tunnelled pleural catheters have a higher success of reliable drainage /pleurodesis of unilateral malignant pleural effusions (62% vs 46%, p=0.064), lower 30 day mortality (8.7 vs 5.9, p-0.036) and longer survival with effusion control (83% vs 52%, p=0.024).[13] Median hospital stay is less with a tunnelled pleural catheter, with a significant improvement in quality of life (p=0.02).[14] Dyspnoea scores and quality of life scores are improved post insertion of tunnelled pleural catheters.[15]

Pleuroscopic pleurodesis with insertion of a tunnelled pleural catheter minimises hospital length of stay. There is an improvement in dyspnoea scores and performance indexes post procedure.[16][17] Freeman et al also found a shorter length of stay with tunnelled pleural catheter compared to traditional talc poudrage (6 days vs 3 days, p<0.0017). There was a shorter time from surgery to systemic therapy with a tunnelled pleural catheter compared to talc poudrage (17 days vs 9 days, p<0.0001).[18]

2.61.1.1.3 Use of intrapleural streptokinase for multiloculated malignant pleural effusions

Saydam *et al*, in a randomised controlled trial, found a significant improvement in mean drainage in patients receiving streptokinase compared to control. There was no significant difference in recurrence rate of pleural fluid.[19]

2.61.1.1.4 Intercostal catheter drainage plus sclerosant instillation

To achieve pleurodesis using the catheter/sclerosant approach, 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 beyond 24-48 hours may not increase the chance of successful pleurodesis [20] and the practice of leaving the catheter in situ until daily drainage has fallen below a certain volume is not evidence based. Success rate, measured by failure of fluid re-accumulation requiring any further procedure is over 70%.[1][21][22][23] Procedural risks should be low if the procedure is performed following current guidelines that include the use of bedside ultrasound.[24]

The drainage of pleural fluid does not need to be below 300ml per day prior to attempting pleurodesis. The success rate of pleurodesis is not significantly different if pleurodesis is attempted when all fluid has been drained (as per chest radiography) or when daily drainage is less than 300ml per day. This significantly reduces hospital length of stay.[25]

Patients receiving treatment for their malignancy have a significantly longer survival time than those not receiving treatment in conjunction with pleurodesis.[26]

2.61.1.1.5 Recommended catheter size to achieve pleurodesis using an intercostal catheter

Historically, large bore (>20F) catheters were used for pleurodesis. One justification for their continued use after smaller, tube over guide-wire, catheter systems became available was that smaller tubes might become blocked by the talc slurry or viscous pleural drainage. Talc slurry will pass through 12F catheters and the blockage rate of size 8F-12F tubes even when used for drainage of empyema was 8% and even lower in non-infected effusions.[27] Intercostal catheters larger than 20F, as traditionally used, may not increase the success rate but may increase complications and pain. Catheters in the range 12-14F may be as effective as larger tubes.[28][29][30][26]

2.61.1.1.6 Pigtail Catheter versus intercostal tube for pleurodesis of malignant pleural effusions

Ghoneim *at al* compared pigtail catheters versus intercostal tubes for pleurodesis of malignant pleural effusions. 66% of patients in the pigtail catheter arm compared to 54% of patients in the intercostal catheter arm achieved pleurodesis, p=0.22). There was a significantly higher complication rate in the intercostal tube arm compared to the pigtail catheter arms (86% vs 44%, p<0.0004).[31] Srour *et al* found a significant improvement in pleural effusion control (OR 2.1 95% CI 1.2-3.7), as well as significant improvement in survival time and effusion free time.[32]

2.61.1.1.7 VATS talc pleurodesis versus bedside intercostal catheter pleurodesis

Terra et al[33] randomised 60 patients with recurrent MPE (17 with NSCLC), >90% expansion after thoracentesis and KPS > 70% to VATS talc poudrage under general anesthesia versus bedside chest tube and talc slurry. Patients who underwent VATS talc poudrage more often had complete postoperative lung expansion than those who received talc slurry administered through a chest tube (60% versus 30%, [p = 0.027]). Whilst the authors emphasise that no difference was found in quality of life or requirement of re intervention between the groups, no power calculation was reported with regard to these outcomes and as such a negative result is difficult to interpret. There was a trend toward incomplete initial re expansion being associated with both clinical recurrence (2/27 versus 7/33 [p=0.15]) and complication (5/27 versus 11/33 [p=0.20]).

Yim et al[34] randomised 57 patients (33 with NSCLC) to VATS talc insufflation under general anesthesia versus talc slurry at the bedside. There was no statistically significant difference between the two groups of patients with respect to chest drainage duration, post procedural hospital stay, parenteral narcotic requirement, complications, or recurrence (1/28 versus 3/29 [NS]). No power calculation was reported.

Dressler et al[22] randomised 482 patients (182 with NSCLC) to VATS with talc insufflation under general anesthesia (TTI) versus bedside chest tube and talc slurry. Thirty day freedom from radiographic recurrence among surviving patients whose lungs initially re-expanded > 90% favoured VATS, but did not reach significance (78% versus 71% [NS]). Patients with primary lung or breast cancer had statistically significantly higher success with TTI than with TS (82% versus 67% [p = 0.022]). Respiratory complications were more common after TTI (13.5% versus 5.6% [p = 0.007]). There was no difference in mortality. Patient perceptions of pain control (p = 0.07), comfort (p = 0.019) and medical safety (p = 0.013) favoured TTI. Fatigue was significantly better after TTI (p = 0.016).

Three meta analyses have addressed rate of recurrence of MPE after VATS talc pleurodesis versus bedside chest tube and talc slurry. Two found in favour of VATS and one found no difference between the two groups. Tan *et al*[35] found a relative risk (RR) of 0.21 (95% CI 0.05 – 0.93) if VATS was employed and Shaw et al[1] a RR of 1.19 (95% CI 1.04 to 1.36) if bedside chest tube and talc slurry were employed. Shaw also reported data for mortality based on four studies and 127 patients comparing thoracoscopic versus bedside instillation of various sclerosant. There was no difference in mortality amongst the participants with RR = 1.36 (95% CI 0.88 to 2.10). Unfortunately neither meta analysis included the results of the largest RCT to date.[23]

Mummadi *et al* had a RR of 1.06 (95% CI 0.99 to 1.14) when comparing talc slurry to talc insufflation. Respiratory complications were less in the talc insufflation groups with a RR of 1.91 (95% CI 1.24 to 2.93).[36] VATS has the advantage of assessing the likelihood of adequate re expansion to achieve talc pleurodesis and failing this may facilitate the intra operative decision to decorticate or more likely place a long term catheter. The procedure is performed under sterile conditions, with general anaesthesia and peri operative pain service support. This compares favourably from the patient's perspective to bedside insertion of tube under local anaesthetic.[34] Further, tissue biopsy provides histological confirmation and potentially molecular information, which may be important to ongoing management.

Likely increased cost (though no study has addressed the impact of repeat procedures in failed pleurodesis), pressure on operating theatre time and requirement of admission are disadvantages when compared to long term indwelling catheters, which may be inserted in an outpatient setting. Disadvantages of long term indwelling catheters include patient preference, long term consumable expense and requirement for long term nursing support.

Basso *et al* studied 46 patients undergoing Videoassisted thoracoscopic talc pleurodesis to assess improvement in quality of life in symptomatic malignant pleural effusions. Karnofsky Index and MRC dyspnoea score were both significantly improved post-operateively, p=0.014 and p<0.001 respectively.[37]

2.61.1.1.8 VATS decortication versus VATS pleurodesis

VATS decortication has not been the subject of a RCT, but mortality has been as high as 13% and prolonged air leak 20% in case series.[35]

2.61.1.1.9 Use of single incision thoracoscopic pleurectomy

A case series involving 19 patients undergoing single incision pleurectomy demonstrated a success rate of 91.4%. Median chest tube removal time was 2 days.{{Cite footnote|Citation:Kara M, Alzafer S, Okur E, Halezeroglu S 2013}

2.61.1.1.10 Intubated vs nonintubated VATS pleurodesis

There is no difference in pleurodesis success rate between intubated nonintubtaed VATS pleurodesis. Operating time, postoperative hospital stay, postoperative mortality, costs and quality of life were all better in the nonintubated VATS pleurodesis group. There is no difference in effusion free and overall survival.[38]

2.61.1.1.11 VATS talc pleurodesis versus tunnelled pleural catheter

Tunnelled pleural catheter has a significantly shorter mean length of stay (7 days vs 8 days, p=0.006), post procedure length of stay (3 days vs 6 days, p<0.0001) and less reinterventions required (1 vs 8, p=0.01) compared to VATS talc pleurodesis. There is no difference in complications, readmission for ipsilateral effusion or in-hospital mortality.[39]

2.61.1.1.12 Optimal 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%.[40] A 2013 study in Japan, demonstrated the efficacy of thoracocsocpic talc poudrage to be 100% at 180 days post procedure, and 71.1% in patients having talc slurry pleurodesis.[41] 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.[42] Justification for the use of talc as preferred

sclerosant is derived from a meta-analysis that compared the relative efficacy of six sclerosants (talc, bleomycin, tetracyclines, corynebacterium parvum, mitozantrone, mepacrine) for pleurodesis. Particular emphasis was placed on talc, bleomycin and tetracycline as these sclerosants are most frequently used in clinical practice and were also the most extensively evaluated in these RCTs. The meta-analysis demonstrated that talc was the most effective sclerosant, with a relative risk for success of pleurodesis of 1.34 (95%CI 1.16 to 1.55). The efficacy of talc relative to bleomycin and tetracycline favoured talc as the sclerosant for successful pleurodesis (RR 1.23, 95%CI 1.00 to 1.50). Talc, compared with all other sclerosants as controls, had a number needed to benefit (NNTB) of 5 (95% CI 3.31 to 9.71).[1]

A meta-analysis of talc pleurodesis demonstrated a RR of 1.21 (95% CI 1.01 to 1.45) for talc pleurodesis compared to control. For thoracoscopic talc poudrage versus control the RR was 1.74 (95% CI 1.11 to 2.73) and talc slurry versus control the RR was 1.05 (95% CI 0.87 to 1.27). Talc was superior to bleomycin for pleurodesis (RR 1.25, 95% CI 1.06 to 1.46).[43]

A systematic review of six observational trials supports Iodopovidone as a safe and effective pleurodesis agent with the success rate of pleurodesis varying from 64.2% to 100%.The summary success rate of all the studies was 90.6% (95% confidence intervals [CI], 86.4–93.8). The only significant complication reported was chest pain of varying degree.[44] A randomised controlled trial consisting of 60 patients, investigating the adverse events of Iodopovidone demonstrated 47 serious events in 34 patients. These were mainly chest pain and hypertension. [45] In a case series by Godazandeh *et al*, pleurodesis success with povidone-iodone was 72.2%, with pain being the most common adverse event (35.9%).[46] In other parts of the world, small volume solutions of povidone-iodine have been used and achieve success rates similar to talc.[44][47][48] Iodopovidone is effective when administered via thoracoscopy or intercostal catheter. Only small volumes of iodine as reported in published papers should be used, as iodine toxicity can occur with larger instillations (up to 500mls).[44]

A randomised controlled trial comparing autologous blood pleurodeis to tetracycline pleurodesis in malignant pleural effusion demonstrated equivalent efficacy (83.4% vs 87.5%, p=0.37). Autologous blood pleurodesis had fewer complications (pain score p<0.01 and fever p<0.01). Total hospital stay was shorter in the autologous blood pleurodesis group (8.2 days vs 9.8 days, p=0.04).[49]

Gaafar *et al* performed a randomised controlled trial compared mistletoe preparation to Bleomycin as palliative treatment for malignant pleural effusion. There was no difference in clinical response (61.5% vs 30%, p=0.2138) or toxicities.([50]

A case series by Menna *et al* using silver nitrate as a sclerosant following failed thoracoscopic talc poudrage showed a significant reduction in fluid drainage with no difference in hospital stay.[51] Adverse events are predominantly metabolic and hypoxia.[52]

Vandetanib, a vascular endothelial growth factor inhibitor, was combined with an intrapleural catheter by Massarelli et al to determine whether this reduces time to pleurodesis.[53] They did not find any significant reduction to time in pleurodesis.

2.61.1.1.13 Intrapleural hyperthermic perfusion chemotherapy versus talc pleurodesis or pleurectomy/decortication

The median survival is longer in patients undergoing Intrapleural hyperthermic perfusion chemotherapy compared to talc pleurodesis and pleurectomy/decortication (median survival 15 months vs 6 months vs 8 months). There was no significant difference in adverse events.[54] Back to top

Evidence summary	Level	References
Talc slurry or povidone-iodone solution may be instilled using a small bore 12-14F catheter. There may be no benefit from larger catheters. Last reviewed December 2015	II, III-1, III-3	[28], [29], [30], [26]

Evidence-based recommendation	Grade
Smaller-bore, 12-14F, intercostal catheters may be used for bedside pleurodesis in patients with malignant pleural effusions. Last reviewed December 2015	**C**

Evidence summary	Level	References
Indwelling pleural catheters reduce hospital length of stay, improve quality of life and provide superior effusion control to bedside pleurodesis. Last reviewed December 2015	II, III-2, IV	[10], [13], [18], [14], [39], [15], [32]

Evidence-based recommendation	Grade
Indwelling pleural catheters might be effective in the outpatient management of malignant pleural effusion.	**C**

Evidence-based recommendation	Grade
Last reviewed December 2015	

Evidence summary	Level	References
In patients with NSCLC, VATS talc pleurodesis under general anesthesia is superior to bed side chest tube talc pleurodesis in terms of radiological recurrence. Last reviewed December 2015	I, II	[1], [22], [35]
VATS talc pleurodesis under general anesthesia is superior to bed side chest tube talc pleurodesis in terms of patient perception of pain, comfort and safety. Last reviewed December 2015	II	[22]

Evidence-based recommendation	Grade
VATS talc pleurodesis is recommended in fit (ECOG 0-2) patients with NSCLC with an expected survival of >2 months who have >90% lung expansion after needle thoracocentesis. Last reviewed December 2015	**A**

Evidence-based recommendation	Grade
VATS talc pleurodesis may be considered in fit (ECOG 0-2) patients with NSCLC with an expected survival of >2 months who have <90% lung expansion after needle thoracocentesis. VATS with biopsy and subsequent talc pleurodesis may be considered in patients who require pathological confirmation of their cancer to determine management. Last reviewed December 2015	**C**

Evidence summary	Level	References
Cytoreductive therapy with intrapleural hyperthermic perfusion chemotherapy improves survival in patients with malignant pleural effusions. Last reviewed December 2015	II	[1], [20], [21], [22], [23], [47], [54]

Evidence-based recommendation	Grade
Intrapleural Hyperthermic Perfusion Chemotherapy (HIPEC) could be used in the treatment of malignant pleural effusions. Last reviewed December 2015	**C**

Evidence summary	Level	References
Pleurodesis using an intercostal catheter and injection of sclerosant is an effective and safe alternative to VATS procedures albeit with a somewhat lower success rate. Last reviewed December 2015	I, II, III-3, IV	[11], [45], [36], [43], [1], [20], [21], [22], [23], [47]

Evidence-based recommendation	Grade
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. Last reviewed December 2015	**A**

Practice point

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 December 2015

Practice point

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 December 2015

Practice point

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 December 2015

Practice point

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 December 2015

Practice point

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

Last reviewed December 2015

Practice point

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 December 2015

Practice point

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

Last reviewed December 2015

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.

Last reviewed December 2015

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2.62 Case management

Contents

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 chalenges of having cancer.[1] 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 in 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 a 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 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[2] 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[3] (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,[4] small proportions of lung cancer subjects,[5][6] in addition to the challenge of determining what aspect of a multi-pronged intervention had a specific effect.

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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.[7] Given that Australian studies have shown low[8] and inconsistent[9] 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.

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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.[10] 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.

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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. Last reviewed October2015

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. Last reviewed October2015	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. Last reviewed October2015	**B**

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2.63 Treatment of rash from anti-EGFR therapy

Contents

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[1] and gefitinib2, and a monoclonal antibody cetuximab[2] 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.[3] 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.[4]

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.[5]

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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.[6] The combination of lymecyline and a non-steroidal skin moisturiser reduces severity, although increasing the frequency of low grade rash in colorectal and lung cancer patients receiving Cetuximab or Erlotinib.[7] 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.[8] 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.[9]

Patients receiving Panitumumab (a monoclonal antibody targeteting EGFR) and concurrently commenced prophylactically applying a moisturiser in addition to Minocycline found it to be superior to the reactive management treatment plan when treating colorectal cancer patients.[10] Vitamin K cream for the prophylaxis of rash in colorectal patients has a lack of convincing data, with limited or no efficacy.[11][12] Sunscreen does not prevent rash.[13]

It is unclear to what extent the individual interventions of antibiotics and moisturisers, contributes to prophylactic rash management when used in combination and data is lacking as to which moisturisers are superior and how often to apply.

Quality of life data suggest the daily use of multiple skin moisturisers is acceptable to patients for the purpose of reducing skin toxicity.[7]

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.

Last reviewed December 2015

Practice point

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 December 2015

Practice point

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

Last reviewed December 2015

Practice point

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 December 2015

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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,[14] 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.[5]

Practice point

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

Last reviewed December 2015

Practice point

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

Last reviewed December 2015

Practice point

Topical formulations of steroids and tacrolimus do not add to the benefit of antibiotic treatment.

Last reviewed December 2015

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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, generally an emollient.[15] 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. Last reviewed December 2015

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2.63.1.5 Other adverse skin and eye effects

Other skin adverse effects including paronychia are seen and are important.Grading of paronychia is related to the extent to which it impacts patient lifestyle. Lack of robust evidence limits recommendations however expert consensus suggests where no infection present, the preferred treatment is topical steroids combined with systemic antibiotic treatment. In severe cases with suspected infection, swab to be taken, and refer to dermatologist.[15]

Ocular side-effects including but not limited to drying of secretions, conjunctivitis, blepharitis and eyelash misgrowth are also described and can be clinically significant.

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2.63.2 Evidence summary and recommendations

Evidence summary	Level	References
Prophylactic antibiotic treatment may reduce the severity or frequency of rash.	II	[6], [8], [9]

Evidence summary	Level	References
Last reviewed December 2015		

Evidence-based recommendation	Grade
A tetracycline can be prescribed in conjunction with anti-EGFR therapy, as it may reduce the severity and frequency of rash. Last reviewed December 2015	C

Practice point

Patients with clinically significant rash may be commenced on oral antibiotic therapy with tetracycline, minocycline or doxycycline.

Last reviewed December 2015

Practice point

The treatment for paronychia is based on expert opinion as no randomised controlled trials have evaluated the therapies.

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.

In severe cases and signs of infection, it is recommended to swab, treat with appropriate systemic antibiotic and refer to dermatologist.

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2.63.4 Appendices

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

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2.63.5 Further resources

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2.64 Guideline development

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.

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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

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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 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 first-line chemotherapy regimen in patients with stage IV inoperable NSCLC?
- Is carboplatin based chemotherapy as effective as cisplatin based chemotherapy for treatment of stage IV inoperable NSCLC?
- Which new agent or platinum combination regimen is best for treatment of stage IV inoperable NSCLC?
- Is monotherapy with new third generation (3G) agents as effective as platinum combination therapy for treatment of stage IV inoperable NSCLC?
- Are three chemotherapy agents better than two chemotherapy agents for treatment of stage IV inoperable NSCLC?
- Are non-platinum doublet chemotherapy regimens as effective as platinum doublet regimens for treatment of stage IV inoperable NSCLC?
- What is the optimal duration of first-line chemotherapy for treatment of stage IV inoperable NSCLC?
- Is chemotherapy with a biologic or targeted therapy superior to chemotherapy alone in unselected patients for treatment of stage IV inoperable NSCLC?
- What is the optimal chemotherapy regimen for overall quality of life for patients in the treatment of stage IV inoperable NSCLC?
- What is the optimal first-line maintenance therapy for treatment of stage IV inoperable NSCLC?
- What is the optimal second-line therapy in patients with stage IV inoperable NSCLC?
- What is the optimal third-line therapy in unselected patients with stage IV inoperable NSCLC?
- What is the optimal systemic therapy regimen for patients with poor performance status for treatment of stage IV inoperable NSCLC?
- What is the optimal systemic therapy regimen for elderly patients for treatment of stage IV inoperable NSCLC?
- What is the optimal systemic therapy regimen in selected patients for treatment of 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 optimal management of malignant pleural effusions?
- 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?

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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 where 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.

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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.

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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
I	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
		A study of test accuracy with: an independent, blinded			

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
II	A randomised controlled trial	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
III-1	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)
III-2	A comparative study with concurrent controls: ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study ■ Interrupted time series with a control group	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: ■ Non-randomised, experimental trial ■ Cohort study ■ Case-control study
III-3	A comparative study without concurrent controls: ■ Historical control study ■ Two or more single arm study	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ■ Historical control study

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
	■ Interrupted time series without a parallel control group				■ Two or more single arm study
IV	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.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

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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**
Volume of evidence [1**]	one or more level I studies with a low risk of bias or several level II studies with a low risk of bias	one or two level II studies with a low risk of bias or a systematic review /several level III studies with a low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies /systematic reviews with a high risk of bias
Consistency [2**]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
	population/s studied in body	population/s	population/s studied in body of evidence differ	population/s studied in body of evidence

Component of Recommendation	Recommendation Grade			
	A Excellent	B Good	C Satisfactory	D Poor
Generalisability	of evidence are the same as the target population for the guideline	studied in the body of evidence are similar to the target population for the guideline	to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	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

[1] Level of evidence determined from level of evidence criteria

[2] If there is only one study, rank this component as 'not applicable'

[3] For example results in adults that are clinically sensible to apply children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

[**] For a recommendation to be graded A or B, the volume and consistency of evidence must also be graded either A or B!

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009.[1] (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
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution
PP (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.[1] (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

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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

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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.

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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>

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2.65 Working party members and contributors

Working party members and contributors

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2.66 Conflict of interest register

Competing interest declarations and management

Working Party Members were asked to declare in writing, any interests relevant to the guideline development, prior to commencement. Members were asked to update their information if they became aware of any changes to their interests.

All declarations were added to a register of interests as listed below. The register was made available to the Working Party throughout the development of the guideline, allowing members to take any potential conflicts of interest into consideration during discussions, decision making and formulation of recommendations.

If Working Party Members were identified as having a significant real or perceived conflict of interest, the Chair could decide that the member either leave the discussion whilst the specific area they were conflicted in was discussed or the member could remain present but not participate in the discussion, or decision making on the specific area where they were conflicted. There were no instances where this occurred during the development of this guideline.

The guidelines have now entered the updating phase. Guideline working party members are responsible to update their conflict of interest statements if a new interest arises. The members will receive a formal reminder to review their statements and ensure it is up-to-date prior to the yearly meetings that will be scheduled to review all updates.

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 FAChPM	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.

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	Received sponsorship from Roche, Novartis and Sanofi-Aventis to attend scientific meetings. Received a grant from Merck Serono to conduct a clinical trial. Involved as a consultant and in an advisory capacity by Roche. Nature of input: appraised literature regarding role of chemotherapy in stage IV lung cancer.
Prof Matthew Peters MD FRACP	No competing interest to declare in the currency of the Working Group that are directly relevant to its work in the nominated time span. Received honoraria for CME lectures from AstraZeneca and Boehringer Ingelheim for presentations not related to lung cancer.
	Sat on Advisory Boards for the following companies during 2010-2011:

Working party member	Competing interest declaration
Professor David Ball MB BS, MD, FRANCZR	Lilly Oncology, Boehringer- Ingelheim,Astra Zeneca and Pfizer. Received funding to attend ASCO Chicago 2010 from Boehringer-Ingelheim.
Professor Michael Brown MBBS PhD FRACP FRCPA	Melanoma Advisory Boards for GSK, BMS, and Roche Prostate Cancer Advisory Board for Bayer Research support from Novartis Travel sponsorship from Eli Lilly Educational grant from BMS

2.67 Abbreviations

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	Carboxyaminotriazole
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
NNTB	Number needed to benefit
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	Transcathether 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