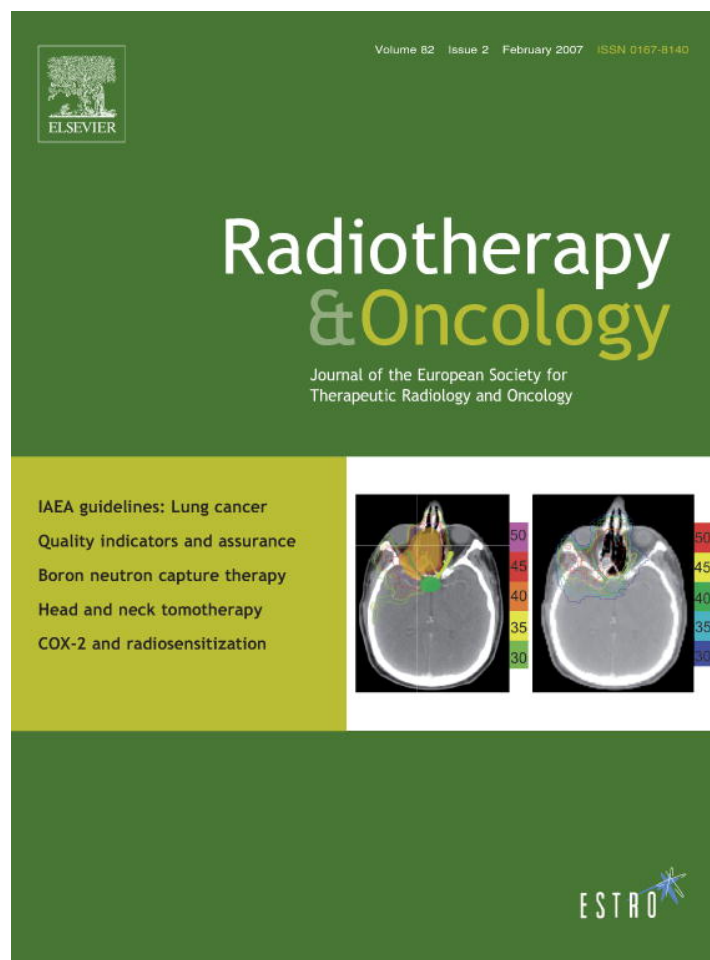


Provided for non-commercial research and educational use only.  
Not for reproduction or distribution or commercial use.



This article was originally published in a journal published by Elsevier, and the attached copy is provided by Elsevier for the author's benefit and for the benefit of the author's institution, for non-commercial research and educational use including without limitation use in instruction at your institution, sending it to specific colleagues that you know, and providing a copy to your institution's administrator.

All other uses, reproduction and distribution, including without limitation commercial reprints, selling or licensing copies or access, or posting on open internet sites, your personal or institution's website or repository, are prohibited. For exceptions, permission may be sought for such use through Elsevier's permissions site at:

<http://www.elsevier.com/locate/permissionusematerial>

## IAEA clinical guidelines

# Lung cancer management in limited resource settings: Guidelines for appropriate good care

Fergus R. Macbeth<sup>a,\*</sup>, Raymond P. Abratt<sup>b</sup>, Kwan H. Cho<sup>c</sup>, Richard J. Stephens<sup>d</sup>,  
Branislav Jeremic<sup>e</sup>, for the International Atomic Energy Agency

<sup>a</sup>National Collaborating Centre for Cancer, Cardiff, UK, <sup>b</sup>University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa, <sup>c</sup>Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea, <sup>d</sup>Medical Research Council Clinical Trials Unit, London, UK, <sup>e</sup>International Atomic Energy Agency, Vienna, Austria

---

### Abstract

Lung cancer is a major cause of cancer death worldwide and is becoming an increasing problem in developing countries. It is important that, in countries where health care resources are limited, these resources are used most effectively and cost-effectively. The authors, with the support of the International Atomic Energy Agency, drew on existing evidence-based clinical guidelines, published systematic reviews and meta-analyses, as well as recent research publications, to summarise the current evidence and to make broad recommendations on the non-surgical treatment of patients with lung cancer. Tables were constructed which summarise the different treatment options for specific groups of patients, the increase in resource use for and the likely additional clinical benefit from each option. These tables can be used to assess the cost-effectiveness and appropriateness of different interventions in a particular health care system and to develop local clinical guidelines.

© 2006 Elsevier Ireland Ltd. All rights reserved. Radiotherapy and Oncology 82 (2007) 123–131.

**Keywords:** Lung cancer; Radiotherapy; Chemotherapy; Clinical guidelines; Limited resource settings

---

Lung cancer is the most common cancer globally with, in 2002, 1.35 million new cases *per annum*, or 12.4% of all new cancers [39]. It is also the most common cause of death from cancer, with 1.18 million deaths, or 17.6% of the total [39]. We have already seen a geographical shift in incidence because of changing patterns of tobacco use in the developing world. In 1980 the proportion of lung cancer in the developing world was 31%, but in 2002 this had risen to 50%, a trend which is set to continue [16].

Developing countries have markedly fewer resources than the developed world. The richest 20% of the world's population uses 83% of the world's resources while the poorest 60% of the population only uses 5% [54]. Even in developed countries, resources may be unevenly distributed, with relative lack of resources in some communities. For instance, the acquisition of megavoltage equipment per unit of population (100,000 people) is proportional to a country's per capita gross national income, resulting in less per capita availability of such equipment in poorer countries [29]. Therefore, many cancer patients will not have access to treatments which are standard elsewhere. The importance of radiotherapy in treating cancers, including lung cancer, in developing countries has recently been highlighted [7].

This document has been prepared by a technical group organised and coordinated by the International Atomic

Energy Agency (IAEA). Its aim is to help oncologists who care for lung cancer patients in limited-resource settings as they formulate their own local guidelines. We hope that it will make it easier to estimate the cost-effectiveness of treatments which require more resources than those of the baseline reference regimens. Decisions about local priorities can then be made on the basis of evidence, rather than on personal bias, fashionable practice or the influence of commercial interests. The document may also help oncologists working where resources are limited to lobby for better resources.

A minimum baseline of personnel, organisation, associated services (e.g. pathology and diagnostic radiology) and specialised equipment is required for the safe practice and development of oncology services. Although the appropriate treatment of all lung cancer patients should be considered whatever the resources available, management where the facilities are below a basic threshold is outside the scope of this paper. We consider a baseline level of non-surgical treatment facilities to be at least cobalt megavoltage therapy with two-dimensional planning and outpatient chemotherapy with conventional agents.

We have tried to identify baseline reference treatment regimens, which can be delivered by an oncology service with access to these basic resources, and then to describe the incremental resources needed, as well as the risks and

benefits to the patients of more sophisticated, and often more intensive therapy. We have not tried to cost these different therapeutic options; costs will vary depending on such factors as international exchange rates and salaries. Capital equipment and drugs are often relatively expensive in developing countries, because these are at international rates, while salaries will be at local rates and less costly.

A difficulty, which we freely acknowledge, is that almost all the research, especially that involving new techniques, equipment and drugs, has been carried out in countries where resources are generally not limited. Therefore the interpretation and application of this evidence have to be based on judgements about the transference of treatment techniques to other situations.

Guidelines are not prescriptive and should not be used to replace clinical experience and judgement. Individual patient evaluation is a very important part of lung cancer treatment, and clinical decisions must always take into account the patient's fitness for treatment, their performance status (PS) and the presence of co-morbidities.

## Methods

The authors met for a two-day consultant meeting at the IAEA (March 9–10, 2006) during which the methods of working were agreed, and the main approaches were drafted. Reference was made to recent English language clinical guidelines [6,36,40,52] which included robust and systematic reviews of the research evidence. This evidence was supplemented by other recent systematic reviews, meta-analyses and research. Following the meeting drafts were circulated sequentially around the group members.

We have assumed that adequate pathological and diagnostic resources are available to enable patients to be grouped according to histology and stage.

## Small cell lung cancer (SCLC)

Patients with SCLC are divided into those with limited disease (LD), usually defined as 'disease that is confined to a hemithorax and regional nodes that can be encompassed in a reasonable radiation port' [52], and those with extensive disease (ED). The minimum diagnostic tests to establish stage are clinical examination, chest X-ray, liver function tests and liver ultrasound (US). If these show that the patient has extensive disease, there is no justification for a CT scan. However, CT of the chest and upper abdomen is a more accurate method of determining the disease extent, if easily available. Isotope bone scan and CT (or MRI) of brain should only be used if there are clinical indications. It may be useful to use the above results, as well as those of the assessment of performance status (PS), serum sodium and lactate dehydrogenase (LDH), to assess the patient's likely prognosis using a recognised prognostic score [12]. Intensive potentially curative treatment should only be considered for patients found to have a good prognostic score.

### Limited disease SCLC

SCLC is chemo-sensitive. In 1978 the use of combination chemotherapy with cyclophosphamide, doxorubicin and vin-

cristine for patients with limited SCLC resulted, historically, in a response rate of 75% and an increase in survival, compared to untreated patients, from 3 to 12 months [30].

The current reference regimen is cisplatin and etoposide (PE) which is highly active in patients with SCLC. A trial comparing PE to a non-platinum combination regimen, in patients with both limited and extensive disease, found an increase in median survival from 9.7 to 14.5 months ( $p=0.001$ ) and a 12% increase in absolute survival with the cisplatin containing regimen at 2 years [55]. A meta-analysis has shown that improvement with cisplatin, in patients with both LD and ED, is independent of the administration of etoposide with an increase in 1 year survival of 4.4%, an odds ratio (OR) of 0.8 and  $p=0.002$  [46].

Consolidation radiotherapy to the chest, given after chemotherapy, has been shown to further improve survival rates in patients with LD SCLC. A meta-analysis showed a 14% reduction in death rate ( $p=0.001$ ), a relatively larger reduction in younger compared to older patients. The absolute survival benefit was 5.4% at 3 years. [41,42]. Chest radiotherapy can be given as parallel opposed AP/PA fields planned on a simulator, treating the mediastinum and site of tumour with regimens such as 40 Gy in 15 fractions, 45 Gy in 18 fractions or 54 Gy in 27 fractions with dose reduction to the spinal cord, either by use of oblique fields or spinal cord shielding for two or three fractions.

In the past consolidation chest radiotherapy was always given following four or six cycles of chemotherapy. More recently trials have investigated the use of radiotherapy given concurrently with chemotherapy and have consistently reported an increase in the rate of severe oesophagitis with concurrent treatment, especially if anthracycline chemotherapy is given. The timing of radiotherapy in these schedules has also been investigated. Three meta-analyses and systematic reviews on this topic have been published, two of which [18,23] have shown a survival advantage for the early administration of combined radio-chemotherapy, while the third one [14] did not. Current consensus favours the use of concurrent chemo-radiotherapy schedules in which the radiotherapy is given early.

A twice daily, hyperfractionated accelerated chemo-radiotherapy schedule, with 45 Gy given in 30 fractions over 3 weeks, has also been shown to increase overall survival [59], but this comes with a number of cost and practical issues, as well as a significant further increase in oesophagitis. It is not clear whether the benefit in this trial came from the twice daily regimen itself or because the radiotherapy was accelerated and given over a shorter period than in the very prolonged comparator regimen of 45 Gy in 25 daily fractions over 5 weeks. One systematic review [14] has indicated that better outcomes are associated with a shorter overall treatment time.

Prophylactic cranial irradiation (PCI) following chemotherapy benefits patients with LD SCLC who have had a complete response (CR) to chemotherapy [3,4]. A meta-analysis has shown a reduction in the risk of death of 16% with PCI, which corresponds to a 5.4% increase in survival at 3 years (15.3% in the control compared to 20.7% in the treatment group) [4]. Doses of between 24 and 30 Gy in 2 Gy fractions may be used. Although there is no clear evidence of radiation-induced late neurotoxicity

in the treatment group, PCI should be carefully considered in patients over the age of 75 or with known cerebro-vascular disease.

These recommendations are summarised in Table 1.

### Extensive disease SCLC

In this group of patients all treatment will be palliative, as very few patients are long term survivors. Chemotherapy results in symptom improvement and an increase in median survival from 2 months to 6 months or longer [30]. Patients with a good PS (WHO PS 0–2) should be given chemotherapy with either a platinum or non-platinum-based combination, as the former does not improve survival in this group of patients [55]. Patients with a poor PS (WHO PS 3 or 4) have a high risk of early treatment-related death, but if the clinician and patient both feel that chemotherapy is an option, patients must be carefully monitored, and perhaps given reduced chemotherapy doses initially.

Radiotherapy should be reserved for palliation, or if the patient is unsuitable for chemotherapy.

### Second-line treatment for SCLC

Re-treatment with the same chemotherapy regimen may be considered for patients who relapse more than about 6 months after their first-line chemotherapy. The response rate is approximately half of that seen in chemo-naïve patients. Other regimens can be used if the patient relapses earlier but is still fit for chemotherapy. Palliative RT with regimens as for NSCLC (see Table 5) is always an option.

## Non-small cell lung cancer (NSCLC)

### Stage I and II NSCLC

Surgery offers the greatest chance of cure. It requires a careful risk assessment taking into account whether the tumour is technically operable, and whether the patient is medically fit enough for major surgery.

An initial assessment including a physical examination, full blood count, liver function tests, bone biochemistry and chest X-ray may exclude many patients because of obvious inoperability, metastatic disease or co-morbidity. For the remainder the minimum investigations should be CT scans of thorax and upper abdomen, and a formal assessment of respiratory function. Further investigations such as isotope bone scan and CT (or MRI) brain scan should only be carried out when there are clinical symptoms and/or signs suggestive of metastases to bone or brain. However in view of the high incidence of brain metastases in patients with adenocarcinoma imaging of the brain may be considered.

The currently used staging system largely reflects the prognosis after surgery [35]; T1 disease is less than 3 cm, and N1 disease indicates the presence of hilar nodes. In patients with Stage I disease, the 5-year survival rate for patients with T1N0 disease it is 60% and for T2N0 disease is 38%. In Stage II disease, the 5-year survival rate for T1N1 is 34%, for T2N1 it is 24% and for T3N0 it is 22% [35].

A number of randomised trials have investigated whether post-operative, adjuvant cisplatin-based chemotherapy is beneficial, and these results have been summarised in a recent review [44] and two other meta-analyses which have not yet been fully published [11,43]. Although many of the

Table 1  
Options for patients with limited disease SCLC and good prognosis

Intervention	Additional resources	Additional risks	Additional outcome benefit
Chemotherapy: older agents (e.g. doxorubicin, cyclophosphamide, vincristine)	–	–	–
Chemotherapy: platinum + etoposide	More prolonged iv administration	Renal toxicity, ototoxicity	ASB: 12% at 2 years
Chemotherapy plus sequential consolidation thoracic RT (40–54 Gy in 15–27 fractions)	RT: Simple planning, AP/PA fields, 15–27 daily fractions	Oesophagitis, pneumonitis and fibrosis, neutropenia	ASB: 5% at 3 years
Chemotherapy plus concurrent thoracic RT	RT: complex CT planning, 3 or 4 fields, 20 daily fractions	Oesophagitis, pneumonitis and fibrosis	Possible increase in 5-year survival with short (30 days) RT regimen.
Chemotherapy plus twice daily concurrent thoracic RT (45 Gy in 30 fractions bd)	RT: Complex CT planning, 3 or 4 fields, 30 fractions (twice daily), ?hospital admission	Severe oesophagitis which may require hospitalization; largely depending on the type and administration of chemotherapy	ASB: 10% at 5 years but uncertain when compared to conventional regimen with higher total dose
Chemotherapy plus any of above plus prophylactic cranial RT (in complete responders)	RT: simple planning, lateral fields, 10–15 fractions	Prolonged alopecia, possible impaired cognitive function	ASB: 5% at 3 years

ASB, absolute survival benefit.  
RT, radiotherapy.

trials did not show a statistically significant benefit from adjuvant chemotherapy, the trend generally favoured chemotherapy. The results of the largest trial (IALT) [56] were statistically significant. The 5-year survival rate with surgery was increased from 40% to 45% with a hazard ratio of 0.86 and  $p = 0.03$ . It is therefore likely that there is an absolute survival benefit of around 5% at 5 years. This benefit needs to be counterbalanced by the cost and toxicity of therapy. Although it is likely on the present evidence that patients with pathological Stages II and III will benefit, this is less clear for those with Stage I disease.

A two-drug, platinum-based chemotherapy should be used for 3 or 4 cycles, and there is little evidence that the use of a third generation agent is necessary.

Post-operative radiotherapy appears to be detrimental. The PORT meta-analysis showed worse survival in patients with Stage I and II disease with post-operative irradiation [45], probably because of deaths from late radiation toxicity. This meta-analysis was however based on a number of old trials and RT techniques have improved significantly since. Although the possible benefits are unknown, post-operative RT may be considered for patients with a macroscopic incomplete resection.

These options are summarised in Table 2.

### Medically inoperable Stage I and II NSCLC

Patients with T1N0 or radiological T2N0 disease, who are unfit for surgery because of co-morbidity ('medically inoperable'), should be considered for radical, 'curative' RT. There have been no randomised trials comparing different regimens. A systematic review has summarised the non-randomised studies [49] and there are recent publications [24,28], all of which suggest that this is an effective and worthwhile treatment. In situations where thoracic services are not available or are of questionable standard, this may also be an option for operable patients.

For small tumours (up to 4 cm maximum diameter) a hypofractionated regimen such as 55–60 Gy in 20 daily fractions may be used rather than the conventional regimen of 60 Gy in 30 fractions. Continuous hyperfractionated, accelerated radiotherapy, CHART (54 Gy in 36 fractions over 12 days), has been shown to be safe and more effective than

conventionally fractionated radical radiotherapy in this group of patients [50]. However CHART is difficult to implement because of the logistics of giving radiotherapy three times a day, and over 12 continuous days without a weekend break.

Radiotherapy should be planned taking into account the dose to normal lung and to the spinal cord, with a field arrangement depending on planning capabilities. The use of two parallel opposed fields will mean that the total dose will be limited by spinal cord tolerance. More complex planned field arrangements will increase the dose to the lung, and in these cases radiotherapy should only be given with megavoltage machines following CT scan planning. If a computerised planning system allows measurement of dose volume histograms (DVH), the volume of normal lung receiving 20 Gy (V20) should be kept below 35% and the mean lung dose below 20 Gy, taking into account the patient's measured lung function [21].

These options are summarised in Table 3.

### Favourable Stage III NSCLC suitable for radical non-surgical treatment

Selected patients with a small tumour volume, no malignant pleural effusion, good PS (WHO PS 0-1), weight loss less than 10%, good respiratory function and normal serum biochemistry belong to this group and they should be treated with radical radiotherapy, as described above. The dose to the ICRU point should be in the range of 55 Gy in 20 fractions to 66 Gy in 33 fractions. The 2-year survival rate is between 12.5% and 24% (37). The largest size of tumour for which it is reasonable to consider radical radiotherapy is difficult to define, although larger tumours are associated with a lower chance of local control (see discussion below). Patient selection should be determined by the other prognostic factors and an assessment of whether radiotherapy to a radical dose may result in unacceptable lung toxicity.

Some patients may be suitable for combined chemo-radiotherapy. Radiotherapy may be given after, or concurrently with, 2 cycles of a platinum-based 2-drug chemotherapy regimen (e.g. cisplatin/etoposide). Randomised trials have consistently shown a significant survival advantage in patients treated with sequential chemotherapy-radiotherapy com-

Table 2  
Options for patients with operable NSCLC

Intervention	Additional resources	Additional risks	Additional outcome benefit
Surgery	—	—	—
Surgery plus adjuvant chemotherapy	Chemotherapy: drug costs (cisplatin + another agent) × 4 administration × 4	Alopecia, neutropenic sepsis, renal damage, neuropathy	ASB: 4–5% at 5 years
Surgery plus adjuvant RT	RT: simple planning <sup>a</sup>	Oesophagitis, pulmonary fibrosis, ?cardiac damage	<b>Adverse effect</b> on survival for Stage I and II (presumably due to increased toxicity) and increased local control in Stage III but no change in survival

ASB, absolute survival benefit.

RT, radiotherapy.

<sup>a</sup> RT with complex CT planning may reduce morbidity, but no evidence on survival or late toxicity.

Table 3  
Radiotherapy options for patients with medically inoperable NSCLC (Stage I and II)

Intervention	Additional resources	Additional risks	Additional outcome benefit
Radical RT alone: 55 Gy in 20 fractions	–	–	–
Radical RT alone: 60–66 Gy in 30–33 fractions	Additional 10 fractions and 2-week treatment	? Reduced risk of pneumonitis and oesophageal stricture, if large fields are used	Unknown
CHART (54 Gy in 36 fractions in 12 days)	RT: 16 extra fractions, at least 16 outside normal working hours. Inpatient admission	More radiation oesophagitis	ASB: 9% in 3-year survival compared to 60 Gy/30 F

ASB, absolute survival benefit.  
RT, radiotherapy.

pared to radiotherapy alone [25,38,51], although the size of the effect shown is variable. Although a Cochrane review of randomised trials [48] and a meta-analysis based on individual patient data [5] both suggest that concurrent treatment may be better than radiotherapy alone, the heterogeneity of the trials means that this remains uncertain.

Randomised trials comparing concurrent with sequential chemo-radiotherapy have suggested that concurrent chemo-radiotherapy may give better outcomes [8,19,62] although the evidence is not strong and the survival benefit uncertain. There is however a significant increase in radiation oesophagitis. Such intensive therapy should not be undertaken unless there are adequate resources to manage patients at significant risk of major toxicity.

These options are summarised in Table 4.

Surgery after radiotherapy has not been shown to be better than chemo-radiotherapy in this group of patients [2,60], and so should not be undertaken except as part of prospective research.

#### Unfavourable Stage IIIa and IIIb NSCLC not suitable for radical treatment-radiotherapy

This group consists of patients with extensive mediastinal lymph nodes or bulky T3/T4 tumours, those with other adverse prognostic factors such as a poor performance status, significant weight loss or abnormal serum biochemistry, and those with poor lung function. Treatment is aimed at achieving local control until sub-clinical metastases become obvious, but the tumours are often so large that local

Table 4  
Options for patients with inoperable 'small' volume NSCLC ('Favourable' Stage III)

Intervention	Additional resources	Additional risks	Additional outcome benefit
Radical RT alone: 55 Gy in 20 fractions	–	–	–
Radical RT alone: 60–66 Gy in 30 fractions	Additional 10 fractions and 2 weeks treatment	? Reduced risk of pneumonitis if large fields are used	Unknown
CHART (54 Gy in 36 fractions in 12 days)	RT: 16 extra fractions, at least 16 outside normal working hours. Inpatient admission	More severe radiation oesophagitis – but shorter duration	ASB: 9% in 3 year survival compared to 60 Gy/30 F
Conventional radical RT followed by adjuvant chemotherapy	Chemotherapy: drug costs (cisplatin + another agent) × 4 administration × 4	Alopecia, neutropenic sepsis, renal damage, neuropathy	ASB: 4% at 2 years
Chemotherapy followed by conventional radical radiotherapy (60 Gy in 30 fractions)	Chemotherapy: drug costs (cisplatin + another agent) × 2–4 administration × 2–4	Alopecia, neutropenic sepsis, renal damage, neuropathy, radiation oesophagitis	ASB: probable increase in 2 year survival (5–13%)
Concurrent chemo-radiation	Chemotherapy: drug costs (cisplatin + another agent) × 2–4 administration × 2–4	Neutropenic sepsis, radiation oesophagitis (above worse than with sequential chemo-radiation), alopecia, renal damage, neuropathy	ASB: possible increase in 2 year survival.

ASB, absolute survival benefit.  
RT, radiotherapy.

control is unlikely and growth delay is the only realistic aim. Tumours 3.5 cm in diameter have a local control rate of 50% after radical radiotherapy (50–60 Gy in 20–30 fractions) and 50% of patients with tumours of this size subsequently develop metastases. Larger tumours are associated with significantly poorer results [1].

It is logical to treat patients who already have or are likely to develop significant thoracic symptoms, with local palliative radiotherapy. A recently updated Cochrane review [27] has shown that for good PS patients higher doses of local radiotherapy appear to be associated with longer survival. The largest trial that only recruited good PS patients [33,34] showed a 2-month improvement in median survival and a 5% increase in 1-year survival (36% vs. 31%) for patients treated with 39 Gy in 13 fractions compared to those treated with 17 Gy in 2 fractions. This regimen did not give greater or longer-lasting palliation of local symptoms and was associated with more oesophagitis.

Patients should therefore be considered for treatment with a high dose palliative regimen of radiotherapy to the known thoracic disease. Care should be taken not to exceed the radiation tolerance of the spinal cord when using parallel opposed fields (see Table 5).

These patients may also benefit from chemotherapy in the same way as patients with more advanced disease (see below) but whether there is additional survival benefit over and above that achieved by high dose palliative radiotherapy is unknown.

### NSCLC patients with Stage IIIB and IV disease – chemotherapy

A meta-analysis has shown that cisplatin-based chemotherapy results in a modest survival benefit in patients with Stage III and IV disease and good PS (WHO PS 0,1); there is a 6–8 week increase in median survival and a 10% increase in 1-year survival compared to 'best supportive care' [37]. There may also be an improvement in quality of life. The use of newer and more expensive agents, so-called third generation agents (docetaxel, paclitaxel, vinorelbine, and gemcitabine), appears to improve the outcome. A combination of cisplatin with one of these third generation agents

may improve both the response rate and 1-year survival rate from 20% to 35%, compared to the use of cisplatin with an older agent [10,20,26] although not unequivocally [20]. These figures are, however, largely inferred and not derived from randomised trials with direct comparisons. Some of the apparent improvement in outcome may be due to patient selection and other factors.

Adding a third drug does not further improve these results. A meta-analysis has shown that this does not increase the survival rate but does increase the toxicity with significantly more neutropenia, infection and mucositis with a three-drug combination [15].

Attempts have been made to reduce the toxicity of chemotherapy for NSCLC. The use of one rather than two drugs results in less toxicity but a meta-analysis has shown that there is a significantly lower response rate (13% compared to 26%) and 1-year survival rate (30% compared to 35%) for patients treated with a single drug [15]. The replacement of cisplatin with carboplatin also results in less symptomatic toxicity, but a meta-analysis comparing cisplatin with carboplatin (when combined with third generation agents, such as cisplatin or vinorelbine) has however shown that the response rate and survival are better with cisplatin [22]. Many oncologists have, nevertheless, considered this a worthwhile trade off for the reduced toxicity.

These options are summarised in Table 6.

Cisplatin may also be replaced by a third generation agent with no worsening of the survival rate as shown in a further meta-analysis [13]. This is, however, particularly expensive. There is no obvious benefit from giving more than three or four cycles of chemotherapy [53], but there is a risk of increased toxicity. In patients with poor PS (WHO PS 2 or more), the benefit gained with chemotherapy is likely to be small and it is not recommended.

Patients with significant thoracic symptoms at presentation should be treated with palliative RT, the dose of which will mainly be decided by the patient's PS [27]. Patients with poor PS (WHO PS 2 or 3) should be treated with 10 Gy in a single fraction [9,27,32]. Patients with good PS and thoracic symptoms should receive 16 – 17 Gy in 2 fractions, or, if the modest survival advantage

Table 5  
Options for palliative thoracic radiotherapy

Patients	Dose	Additional resources	Additional risks	Additional outcome benefit
Any	30 Gy in 10 fractions	–	–	–
Stage III (bulky disease, co-morbidity etc.), good PS	39 Gy in 13 fractions	3 extra fractions, spinal cord shielding for 2 fractions	More oesophagitis	ASB: 5% at 1 year compared to 17 Gy in 2 fractions
Any stage, good PS	16 or 17 Gy in 2 fractions	Fewer fractions	Acute chest pains, but less oesophagitis	No worse than 30 Gy in 10 fractions
Any stage, poor PS	10 Gy in 1 fraction	Fewer fractions	Acute chest pains, but less oesophagitis	No worse than 17 Gy in 2 fractions
Any stage, acute stridor	20 Gy in 5 fractions	5 fewer fractions	None but less risk of airway oedema compared to 10 Gy or 17 Gy	Probably no different

ASB, absolute survival benefit.  
RT, radiotherapy.

Table 6  
Options for patients with 'unfavourable' Stage III and Stage IV disease and WHO PS 0 or 1

Intervention	Additional resources	Additional risks	Additional outcome benefit
Supportive care (palliative radiotherapy, opiates, corticosteroids and c)	–	–	–
Chemotherapy: cisplatin + 'older' drugs (e.g. etoposide, ifosfamide, mitomycin)	Drug costs (chemotherapy and antiemetics), iv administration, treatment of anaemia, neutropenia, sepsis, thrombocytopenia	Nausea and vomiting alopecia, anaemia, neutropenia sepsis, thrombocytopenia	6–8-week increase in median survival ASB: 10% at 1 year (10–20%)
Chemotherapy: cisplatin + 'third generation' agent (e.g. vinorelbine, gemcitabine, taxanes)	Increased drug costs	Toxicity much the same	Uncertain ??ASB: 10% at 1 year
Chemotherapy: cisplatin + 2 'third generation' agents	Increased drug costs	More toxicity as above	None
Single 'third generation' agent	Lower drug costs	Less toxicity	1 year survival 5%

ASB, absolute survival benefit.

is thought to be worthwhile, a more prolonged regimen (36–39 Gy in 12–13 fractions). Large fractions of palliative radiotherapy are safe and effective for these patients, and although some may report acute chest pain, fevers and rigors, these are transient [27]. There is a small risk of late spinal cord damage with 17 Gy in 2 fractions, which can be reduced by use of a posterior spinal cord shield. More fractionated regimens (e.g. 20 Gy in 5 fractions) should be used in patients with obvious major airway obstruction and stridor because large fractions may cause more oedema.

Patients with few symptoms at presentation may also be grouped according to their PS. Those with poor PS can simply be watched and given steroids and/or opiates when required and only given radiotherapy if significant local symptoms develop [17]. Those with good PS should be considered for chemotherapy.

### Elderly patients

There is no reason to treat elderly patients differently. Every patient should be judged on their fitness for treatment, taking into account co-morbidities.

### Metastases

Metastases in the bone, brain and spinal cord are common in patients with lung cancer, but all can be well palliated with short courses of (1 or 2 fractions) of radiotherapy [31,47,57,58,61]. Clinical judgement is always required to assess how limited resources might best be used. For example, a patient with brain metastases and poor performance status, or with spinal cord compression and established paraplegia for more than 48 h, is unlikely to gain any benefit from radiotherapy.

### Second-line treatment

Active second-line drugs such as docetaxel, pemetrexed and erlotinib, a tyrosine kinase inhibitor, have been identi-

fied. However the benefits appear small, the agents are expensive and such treatments would only be appropriate where there are ample resources. Re-irradiation may sometimes be possible for selected patients who have had a good response to their initial radiotherapy, and have remained symptom free for a long period (>6 months). The risks of re-irradiation must be clearly understood by the doctor and patient. It is likely that the dose will exceed spinal cord tolerance, particularly because radiotherapy will probably be carried out without CT planning, and using large fractions.

### Supportive care

The majority of patients with lung cancer will not be cured, and a variety of treatment options should be available to ensure that the patient receives adequate supportive and palliative care, not only during treatment, but throughout their illness and to ensure a comfortable end of life period. Treatments can include palliative radiotherapy (often a single fraction can be effective), opiates (for dyspnoea, cough, pain, anorexia and tiredness), and other strategies as determined by clinical judgement and local practice.

### Conclusion

The treatment options outlined above and summarised in the tables represent an interpretation of the current published literature. Readers may disagree with our opinions on specific topics. We believe, however, that they are based on reasonable evidence and do offer a framework for those working in a health care system with limited resources to assess which treatment options are the most appropriate. The tables also could be the starting point for more sophisticated cost-effectiveness calculations using local cost information, which could then be used for prioritisation.

We also advise that robust quality control and clinical audit mechanisms are put in place along with any service development or new technology. Without them the clinical

gains seen in published trials and quoted in this paper are unlikely to be fully realised and there is a risk not only of greater toxicity for patients but also a waste of scarce resources.

\* **Corresponding author.** Fergus Macbeth, Velindre Hospital, Whitchurch, Cardiff CF14 2TL, UK. *E-mail address:* [fergus.macbeth@velindre-tr.wales.nhs.uk](mailto:fergus.macbeth@velindre-tr.wales.nhs.uk)

Received 19 September 2006; received in revised form 5 December 2006; accepted 12 December 2006; Available online 19 January 2007

## References

- [1] Abratt RP. Modelling tumour and treated lung volume influences in the irradiation of non-small cell lung cancer patients. *Int J Rad Oncol Biol Phys* 2001;49:481–5.
- [2] Albain KS, Swann RS, Rusch VR, et al. North American Lung Cancer Intergroup Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309). 2005 ASCO Annual Meeting Proceedings. *J Clin Oncol* 2005;23(16S):7014.
- [3] Arriagada R, Pignon JP, Laplanche A, Le Chevalier T. Prophylactic cranial irradiation for small-cell lung cancer. *Lancet* 1997;349:138.
- [4] Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic cranial irradiation overview collaborative group. *N Engl J Med* 1999;341:476–84.
- [5] Auperin A, Le Pécoux C, Pignon JP, et al. On behalf of the meta-analysis of cisplatin/carboplatin based concomitant chemotherapy in non-small cell lung cancer (MAC3-LC) group concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;17:473–83.
- [6] Australian Government National Health and Medical Research Council: Clinical practice guidelines for the diagnosis and management of lung cancer (2004): <<http://www.nhmrc.gov.au/publications/synopses/cp97syn.htm/>>.
- [7] Barton MB, Frammer M, Shafiq J. Role of radiotherapy in cancer control in low-income and middle-income countries. *Lancet Oncol* 2006;7:584–95.
- [8] Belani CP, Choy H, Bonomi PS, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol* 2005;23:5883–91.
- [9] Bezjak A, Dixon P, Brundage M, et al. Randomized study of single versus fractionated radiotherapy (RT) in the palliation of non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2001;51:20.
- [10] Bonomi P, Kim K, Kusler J, Johnson D. Cisplatin/etoposide vs paclitaxel/cisplatin/G-CSF vs paclitaxel/cisplatin in non-small-cell lung cancer. *Oncology* 1997;11(Suppl. 3):9–10.
- [11] Bria E, Gralla R, Giannarelli D, et al. Pooled analysis of 6494 patients in 12 trials (1994–2004) receiving post-operative adjuvant chemotherapy in non-small cell lung cancer: analyzing the magnitude of benefit in survival. *Lung Cancer* 2005;49(Suppl. 2):42.
- [12] Cerny T, Blair V, Anderson H, Bramwell V, Thatcher N. Pretreatment prognostic factors and scoring system in 407 small-cell lung cancer patients. *Int J Cancer* 1987;39:146–9.
- [13] D'Addario G, Pintilie M, Leigh NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol* 2005;23:2926–36.
- [14] De Ruysscher D, Pijls-Johannesma M, Vansteenkiste J, Kester A, Rutten I, Lambin P. Systematic review and meta-analysis of randomised, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small-cell lung cancer. *Ann Oncol* 2006;4:543–52.
- [15] Debaldo C, Michiels S, Syz N, et al. 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;292:499–500.
- [16] Doll R, Peto R. The causes of cancer. Oxford, UK: Oxford University Press; 1981.
- [17] Falk SJ, Girling DJ, White RJ, et al. Medical Research Council Lung Cancer working party (RP Abratt included). Immediate versus delayed palliative thoracic radiotherapy in patients with unresectable locally advanced non-small cell lung cancer and minimal thoracic symptoms: randomised controlled trial. *Br Med J* 2002;325:465–72.
- [18] Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol* 2004;22:4785–93.
- [19] Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–9.
- [20] Giaccone G, Splinter TA, Debruyne C, et al. Randomized study of paclitaxel-cisplatin versus cisplatin-teniposide in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 1999;17:734–5.
- [21] Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999;45:323–9.
- [22] Hotta K, Matsuo K, Ueoka H, et al. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004;22:3839–41.
- [23] Huncharek M, McGarry R. A meta-analysis of the timing of chest irradiation in the combined modality treatment of limited-stage small cell lung cancer. *Oncologist* 2004;9:6665–72.
- [24] Jeremic B, Shibamoto Y, Acimovic LJ, et al. Hyperfractionated radiotherapy alone for clinical stage I nonsmall cell lung cancer. *Int J Radiat Oncol Biol Phys* 1997;38:521–5.
- [25] Kim TY, Yang SH, Lee SH, et al. A phase III randomized trial of combined chemoradiotherapy versus radiotherapy alone in locally advanced non-small-cell lung cancer. *Am J Clin Oncol* 2002;25:238–43.
- [26] LeChevalier T, Brisgand D, Douillard J-Y, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: Results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994;12:360–7.
- [27] Lester J, Coles B, Macbeth F, Toy E. Palliative radiotherapy for non-small cell lung cancer. *Cochrane Database Syst Rev* 2006.
- [28] Lester JF, Macbeth FR, Brewster AE, Court JB, Iqbal N. CT-planned accelerated hypofractionated radiotherapy in the radical treatment of non-small cell lung cancer. *Lung Cancer* 2004;45:237–42.
- [29] Levin V, Tatsuzaki H. Radiotherapy services in countries in transition: gross national income per capita as a significant factor. *Radiation Oncol* 2002;63:147–50.

- [30] Livingston RB, More TN, Heilbrun L, et al. Small-cell carcinoma of the lung: combined chemotherapy and radiation. A Southwest Oncology Study. *Ann Intern Med* 1978;88:194–9.
- [31] McQuay HJ, Collins SL, Carroll D, Moore RA. Radiotherapy for the palliation of painful bone metastases. *Cochrane Database of Systematic Reviews* 1999; Issue 3. Art. No.: CD001793. <doi:10.1002/14651858.CD001793/>.
- [32] Medical Research Council Lung Cancer Working Party. A Medical Research Council (MRC) randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. *Br J Cancer* 1992;65:934–941.
- [33] Medical Research Council Lung Cancer Working Party. Randomized trial of palliative two-fraction versus more intensive thirteen fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. *Clin Oncol* 1996;8:167–175.
- [34] Medical Research Council Lung Cancer Working Party. Randomised trial of two radiotherapy (RT) policies for patients with inoperable non-small cell lung cancer (NSCLC) and good performance status. *Lung Cancer* 1994;(Suppl. 1):131.
- [35] Mountain CF. Revisions in the international system for staging lung cancer. *Chest* 1997;111:1710–7.
- [36] National Institute for Clinical Excellence (NICE): Clinical guideline 24: The diagnosis and treatment of lung cancer (2005) <<http://www.nice.org.uk/page.aspx?o=cg024fullguideline/>>.
- [37] Non Small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomized clinical trials. *Br Med J* 1995;7:899–909.
- [38] Non-small Cell Lung Cancer Collaborative Group. Chemotherapy for non-small cell lung cancer. *The Cochrane Database of Systematic Reviews* 2000, Issue 2. Art. No.: CD002139. <doi:10.1002/14651858.CD002139/>.
- [39] Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA. Cancer J Clin* 2005;55:74–108.
- [40] Pfister DG, Johnson DH, Azzoli CG, et al. American society of clinical oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–53.
- [41] Pignon JP, Arriagada R. Role of thoracic radiotherapy in limited-stage small-cell lung cancer: quantitative review based on the literature versus meta-analysis based on individual data. *J Clin Oncol* 1992;10:1819–20.
- [42] Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618–24.
- [43] Pignon JP, Tribodet H, Scagliotti GV, et al. on behalf of the LACE Collaborative Group. Lung Adjuvant Cisplatin Evaluation (LACE): a pooled analysis of five randomized clinical trials including 4,584 patients. 2006 ASCO Annual Meeting Proceedings Part I. *J Clin Oncol* 2006;24(18S):7008.
- [44] Pisters KMW, Le Chevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. *J Clin Oncol* 2005;23:3270–8.
- [45] PORT Meta-analysis Trialists Group. Postoperative radiotherapy in non-small cell lung cancer: Systematic review and meta-analysis of individual patient data from nine randomised controlled trials. *Lancet* 1998;352:257–63.
- [46] Pujol JL, Carestia L, Daures JP. Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. *Br J Cancer* 2000;83:8–15.
- [47] Rades D, Stalpers LJ, Veninga T, et al. Evaluation of five radiation schedules and prognostic factors for metastatic spinal cord compression. *Journal of Clinical Oncology* 2005;23:3366–75.
- [48] Rowell NP, O'Rourke NP. Concurrent chemoradiotherapy in non-small cell lung cancer. *The Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No.: CD002140. <doi:10.1002/14651858.CD002140.pub2/>.
- [49] Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable). *The Cochrane Database of Systematic Reviews* 2001, Issue 1. Art. No.: CD002935. <doi:10.1002/14651858.CD002935/>.
- [50] Saunders M, Dische S, Barrett A, et al. on behalf of the CHART steering committee. Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. *Radiother Oncol* 1999;52:137–48.
- [51] Sause W, Kolesar P, Taylor IV S, Johnson D, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest* 2000;117:358–64.
- [52] Scottish Intercollegiate Guidelines Network (SIGN): Management of Patients with Lung Cancer (2005). <<http://www.sign.ac.uk/pdf/sign80.pdf/>>.
- [53] Smith IE, O'Brien ME, Talbot DC. Duration of chemotherapy in advanced non-small-cell lung cancer: a randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. *J Clin Oncol* 2001;19:1336–43.
- [54] Smith R. The champagne glass of world poverty. *BMJ* 1999;318:589.
- [55] Sundström S, Bremnes RM, Kaasa S, Aasebø U, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol* 2002;20:4665–72.
- [56] The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004; 350:351–360.
- [57] Tsao MN, Lloyd NS, Wong RK. Clinical practice guideline on the optimal radiotherapeutic management of brain metastases. *BMC Cancer* 2005;5:34.
- [58] Tsao MN, Lloyd N, Wong R, et al. Whole brain radiotherapy for the treatment of multiple brain metastases. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD003869. <doi:10.1002/14651858.CD003869.pub2/>.
- [59] Turrisi 3rd AT, Kim K, Blum RBI, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265–71.
- [60] van Meerbeeck JP, Kramer G, Van Schil PE, et al. EORTC-Lung Cancer Group. A randomized trial of radical surgery (S) versus thoracic radiotherapy (TRT) in patients (pts) with stage IIIA-N2 non-small cell lung cancer (NSCLC) after response to induction chemotherapy (ICT) (EORTC 08941). 2005 ASCO Annual Meeting Proceedings Part I of II. *J Clin Oncol* 2005;23(No. 16S): 7015.
- [61] Wai MS, Mike S, Ines H, Malcolm M. Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy – a systematic review of the randomised trials. *Cochrane Database of Systematic Reviews* 2004;2:CD004721.
- [62] Zatloukal P, Petruzella L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* 2004;46:87–98.