Chemotherapy and radiotherapy of bronchial carcinoma

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The treatment of lung cancer is important as it represents a global health burden. Many therapies are used including surgery, radiotherapy, chemotherapy, laser therapy, stenting, supportive care and biological agents. Treatment for individual patients is best assessed by a multidisciplinary approach. This article focuses on treatment with chemotherapy and radiotherapy.

Carcinoma of the bronchus is the commonest fatal malignant disease within the UK with about 33 000 new cases per annum (National Institute of Clinical Excellence, 2001). Although there remains a male preponderance, the condition has increased in incidence in women over the years and is now more common than breast cancer. This undoubtedly reflects increased cigarette smoking among the female population, the aetiological role of which is unquestioned in all forms of lung cancer.

Advances have been made in terms of treatment and in the development of strategies and organization, encompassing a multimodality, holistic approach to treatment of the individual. As a result, remissions are achieved and quality of life has improved, but cure rates remain disappointingly low. Important adverse prognostic factors to consider are advanced stage at presentation, poor performance status (PS) (frequently influenced by co-morbidity from other smoking-related diseases) (*Table 1*) and increased age. Delays occur in presentation, investigation and therapy. Unfortunately, a nihilistic approach to treatment is still common.

Chemotherapy and radiotherapy influence both survival and quality of life for patients with all forms of lung cancer. Although they are considered separately here, it will become apparent that multimodality treatment is becoming a common approach.

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TABLE 1.
Performance status

0	Can carry out all normal activities, no restrictions
1	Ambulatory. Can carry out light work, but restricted physical activities
2	Ambulatory. Capable of all self-care. Unable to carry out work. Up and about >50% of waking hours
3	Capable of limited self-care. In bed > 50% of waking hours
4	Confined to bed or chair. Dependent for all care

CHEMOTHERAPY IN LUNG CANCER

Small cell lung cancer (SCLC) is a notoriously proliferative disease, with a propensity to metastasize before clinical detection. It is probably because of the tumour biology that it is also a highly chemosensitive condition and responses to cytotoxic agents (however short-lived) can be anticipated even in advanced stages. For a long time it was thought that non-small cell lung cancer (NSCLC) was relatively insensitive to chemotherapy. It is now known that this is in fact a very useful treatment modality, particularly in the palliation of symptoms of advanced disease, and its use in both the adjuvant and neo-adjuvant settings (*Figure 1*) is continually evolving.

CHEMOTHERAPY FOR SMALL CELL LUNG CANCER

Chemotherapy forms the basis of treatment for almost all patients with SCLC. Remissions are likely, but relapse is inevitable for all but 10–20% of those with limited stage disease (*Table 2*) for whom long-term survival is achieved. Unfortunately, at presentation, most patients will have extensive disease (*Table 3*). Effective palliation of symptoms is still highly achievable, as even bulk disease will respond well in the short term. Over time, most has been achieved in truly limited stage disease, which is unfortunately rare. As a result, clinical trials involving these patients take considerable time to accrue and report.

Combination chemotherapy has been shown to be more effective than the use of single agents.

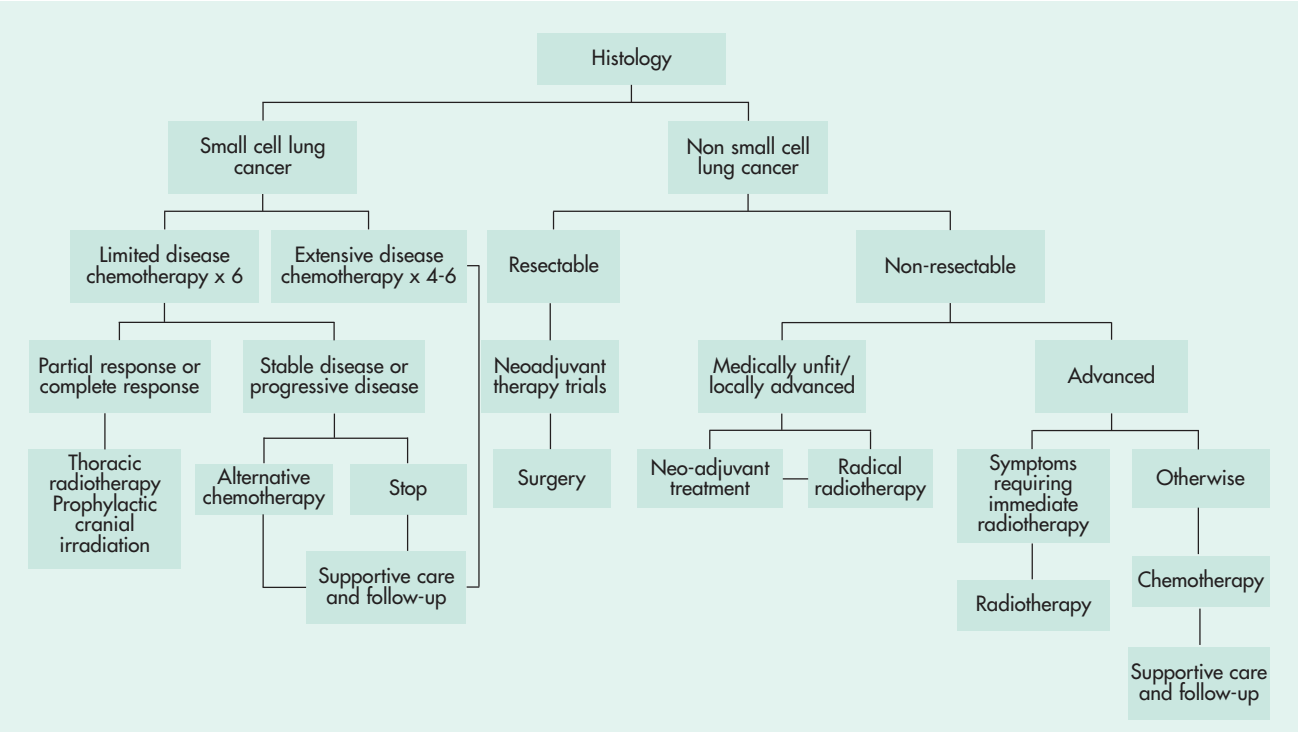

Figure 1. Treatment of lung cancer. Adjuvant therapy = additional treatment (often chemotherapy) given after potentially curative therapy with the aim of reducing relapse rates; neo-adjuvant therapy = treatment given to 'downstage' a tumour to enable potentially curative therapy to be given.

Commonly used regimens are either platinum based, such as PE (cisplatin and etoposide), or anthracycline based, for example CAV (cyclophosphamide, adriamycin and vincristine) and ACE (adriamycin, cyclophosphamide and etoposide). It would appear that carboplatin can be safely substituted for cisplatin, enabling regimens to be more easily given on an outpatient basis. The use of alternating non-cross-resistant regimens does not seem to have resulted in anything other than marginal benefit in either limited or extensive disease. Weekly chemotherapy has no advantage over standard 3-weekly treatment and in terms of duration of treatment, no benefits have been observed when chemotherapy has been continued beyond six cycles. Patients with limited disease and those tolerating therapy with extensive disease in general receive six cycles. For those experiencing marked toxicity, particularly if this necessitates dose reduction, there is likely to be little benefit in continuing beyond four cycles.

Because of its sensitivity to chemotherapy, dose intensification is an attractive concept in SCLC, particularly as preclinical models demonstrate a considerable dose–response relationship. Several mechanisms of increasing dose intensity have been investigated, including:

1. Early intensification (increasing the dose in the first one–three cycles)
2. Where toxicity is a problem, prolonging the interval between treatments rather than reducing the dose
3. Use of growth factors (granulocyte colony-stimulating factor; G-CSF) to reduce the interval between treatments
4. High dose therapy with autologous bone marrow or stem cell transplantation (Humblet et al, 1987; Klasa et al, 1991).

There has been no convincing evidence to support any of these strategies. There is also a significant treatment-related mortality associated with high dose therapy and it is therefore not recommended outside clinical trials, even in limited stage disease.

CHEMOTHERAPY FOR NON-SMALL CELL LUNG CANCER

As approximately 80% of cases of lung cancer are NSCLC and only about 10% of these in the UK are potentially resectable compared with

TABLE 2.
Staging of small cell lung cancer

Limited disease	Disease confined to the ipsilateral hemithorax and supraclavicular lymph nodes
Extensive disease	Any disease beyond limited disease Common sites of metastasis: brain, liver, bone, adrenal glands

15–25% reported in Europe and the USA, any advances made in non-surgical treatment are likely to have widespread implications in public health terms. The initial perception was that chemotherapy would not have a major impact on outcome. Many trials were carried out, but most were too small to be conclusive. Meta-analysis has enabled some broad conclusions to be drawn (Non-Small Cell Lung Cancer Collaborative Group, 1995). More information should soon be available with updates from recent trials. More studies are required, however, particularly regarding more controversial areas.

A simplified summary of the current situation would be that for early stage disease (*Table 4*) more studies are needed to be clear about preoperative and postoperative chemotherapy; in locally advanced disease the addition of chemotherapy to radiotherapy has been shown to be superior to radiotherapy alone and in advanced disease chemotherapy is better than best supportive care. In addition, second-line chemotherapy for NSCLC is now a consideration.

TABLE 3.
Tumour, node, metastasis (TNM) definitions

Primary tumour (T)	TX	Tumour proven by the presence of malignant cells in bronchopulmonary secretions but not visualized by roentgenography or bronchoscopy, or any tumour that cannot be assessed as in a pretreatment staging
	T0	No evidence of primary tumour
	T1S	Carcinoma in situ
	T1	A tumour that is 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy*
	T2	A tumour more than 3 cm in greatest dimension, or a tumour of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumour must be within a lobar bronchus or at least 2 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung
	T3	A tumour of any size with direct extension into the chest wall (including superior sulcus tumours), diaphragm, or the mediastinal pleura or pericardium without involving the heart, great vessels, trachea, oesophagus, or vertebral body, or a tumour in the main bronchus within 2 cm of the carina without involving the carina
	T4	A tumour of any size with invasion of the mediastinum or involving heart, great vessels, trachea, oesophagus, vertebral body, or carina or with presence of malignant pleural effusion†
Nodal involvement (N)	N0	No demonstrable metastasis to regional lymph nodes
	N1	Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension
	N2	Metastasis to ipsilateral mediastinal lymph nodes and subcarinal lymph nodes
	N3	Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, or ipsilateral or contralateral scalene or supraclavicular lymph nodes
Distant metastasis (M)	M0	No known distant metastasis
	M1	Distant metastasis present – specify site(s)

* The uncommon superficial tumour of any size whose invasive component is limited to the bronchial wall and that may extend proximal to the main bronchus is classified as T1. † Most pleural effusions associated with lung cancer are caused by the tumour. There are, however, some few patients in whom cytopathological examination of pleural fluid (on more than one specimen) is negative for tumour and the fluid is non-bloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumour, the cases should be staged T1, T2 or T3, with effusion being excluded as a staging element.

Early stage disease

Following surgery, older trials of adjuvant therapy with alkylating agents are clearly in favour of surgery alone with a 5% reduction in 5-year survival for those treated with chemotherapy. Meta-analysis of studies using cisplatin-based treatments has suggested a survival advantage of the same order at 5 years, but this result is non-significant. The Adjuvant Lung Project Italy study has just reported (Tonato, 2002), showing no benefit from adjuvant chemotherapy. Further trials are soon to report and will hopefully clarify things further. The value of adjuvant chemotherapy following radiotherapy in early disease is also under investigation, with little evidence of benefit as yet. Several small studies have suggested survival benefits from neo-adjuvant (preoperative) chemotherapy and the MRC LU22 study is in progress to determine if this can be confirmed.

Locally advanced disease

Several studies have shown that initial chemotherapy increases the benefits afforded by radiotherapy in locally advanced disease. This effect is independent of the regimen used, although most benefit is again seen in those receiving cisplatin-based therapy.

It is logical to assume improvements in survival to be the result of eradication of

TABLE 4.
Staging of non small-cell lung cancer

Stage	T	N	M
Occult	X	0	0
0	IS	0	0
Ia	1	0	0
Ib	2	0	0
IIa	1	1	0
IIb	2	1	0
	3	0	0
IIIa	3	1	0
	1–3	2	0
IIIb	Any	3	0
	4	Any	0
IV	Any	Any	1

From Mountain (1997)

micrometastases. In practical terms, neoadjuvant treatment is often easier to administer than adjuvant treatment as in general only 40–60% of the planned adjuvant dose is given because of the morbidity associated with the primary management.

Advanced disease

The difficulties encountered when treating patients with advanced NSCLC are predictable, i.e. treating an older population with co-morbid problems impacting on their PS and ability to tolerate toxic treatment. However, with this in mind, the benefits for those with a PS of 2 or less are considerable, both in terms of survival advantage (2 months increase in median survival translating into a 10% improvement in 1-year survival compared with best supportive care) and also importantly, quality of life. For those with a PS of 3 or more, life expectancy is approximately 3 months, i.e. the duration of time spent receiving chemotherapy. Subgroup analysis has not shown that any other patient factors influence the potential gains of treatment.

In terms of the duration of therapy, in a study (Socinski et al, 2001) comparing eight cycles of treatment to four, the median number of cycles in the eight arm was in fact four, as this was the tolerated length of treatment. Another randomized trial (Smith et al, 2001) found no advantage of six over three cycles. Chemotherapy should be discontinued after two cycles if there has been no evidence of response.

Most data have again been obtained from cisplatin-based therapy. Higher doses of cisplatin add toxicity with little or no survival benefit and accumulating evidence shows that carboplatin can be substituted without loss of efficacy. The National Institute for Clinical Excellence has evaluated the evidence concerning the newer agents available for the palliative treatment of NSCLC (National Institute for Clinical Excellence, 2001). In combination with cisplatin, gemcitabine, paclitaxel and vinorelbine have all been approved as first-line agents. No recommendations can be made for one over the other on the basis of the current data. The choice of agent for any individual is therefore likely to reflect economic considerations as well as other factors.

First-line chemotherapy now has a clearly established role in the palliation of NSCLC. As a result, second-line chemotherapy is evolving and in the same evaluation by National Institute for Clinical Excellence, docetaxel has been recommended in this setting, on the basis of randomized trial evidence of survival and quality of life benefit. It is encouraging that such evaluations support the modest improvements in survival and value the improvement in quality of life achieved with modern chemotherapy, particularly as studies show that patients are willing to accept significant toxicity (possibly more than their doctors) for such gains.

RADIOTHERAPY IN LUNG CANCER

High dose (radical) radiotherapy is used with the intention of curing the small number of patients with NSCLC presenting with local disease not proceeding to surgery. Consolidation thoracic radiotherapy, in combination with prophylactic cranial irradiation, is also now standard treatment for patients with limited stage SCLC. More commonly, lower (palliative) doses of radiotherapy are used for control of local symptoms (haemoptysis, cough, breathlessness and pain) in patients with locally advanced and metastatic disease.

RADIOTHERAPY WITH 'CURATIVE' INTENT

Radical radiotherapy *vs* surgery in early stage NSCLC

Surgical resection offers the best chance of cure or long-term survival in early stage (I and II) NSCLC. However, the decision to operate is based not only on the 'resectability' of the tumour (i.e. the stage), but also on the 'operability' (fitness for surgery) of the patient and finally, of equal importance, on the wishes of the patient. Lung cancer patients often have significant co-morbidity such as impaired respiratory reserve from chronic obstructive pulmonary disease or cardiovascular insufficiency, rendering a technically resectable tumour inoperable. Radical radiotherapy is a treatment option for those patients declining surgery and also selective patients unsuitable for resection (Rothwell and Williams, 2001).

It must not be overlooked, however, that poor lung function precluding surgery on the basis of inadequate residual function may also preclude radical radiotherapy because of radiation damage to normal lung tissue. It appears that survival following radical radiotherapy lies somewhere between that of patients treated surgically and palliatively. It is possible that the true difference in survival from patients treated surgically is smaller than the perceived difference, since the factors influencing the decision not to operate are likely to have a detrimental influence on the outcome to alternative treatment. As there has only been one randomized

trial comparing surgery and radiotherapy which was conducted 40 years ago (Morrison et al, 1963), when both staging and radiotherapy techniques were very different, it is difficult to draw definitive conclusions as to their relative effectiveness.

Conventional radical radiotherapy is generally around 60 Gy in 30 fractions of 2 Gy over 6 weeks (Monday to Friday). Improvements in local control could potentially influence survival in early disease. This concept led to the development of the CHART regimen – continuous hyperfractionated accelerated radiotherapy. This regimen delivers 1.5 Gy three times per day, including weekends, for 12 days, aiming to reduce the proliferation of cancer cells between treatments while reducing long-term normal tissue morbidity.

A randomized controlled study of CHART *vs* conventional radiotherapy in localized NSCLC was published in 1997 (Saunders et al, 1997), demonstrating significant improvement in 2-year survival with CHART, at the expense only of increased acute (but not long-term) dysphagia. There are clearly practical aspects which make wide application of CHART difficult. Other methods of improving outcome with conventional radiotherapy are also being explored including hypoxic cell radiosensitization, the use of conformal radiotherapy and the additional use of cytotoxic chemotherapy. In most studies of radical radiotherapy the best outcomes have been observed for those with small tumours, achieving complete radiological responses with a PS of 2 or less and minimal associated weight loss.

Although radical radiotherapy is generally reserved for patients with stage I/II disease, there is a small but significant complete response rate and long-term survival benefit for patients with stage III A and B, i.e. locoregionally advanced disease. Neoadjuvant chemotherapy, with the aim of proceeding to radical radiotherapy, may be of benefit. Concomitant rather than sequential chemoradiotherapy has also been studied in this group of patients. Early results suggest a survival advantage, but at the expense of increased toxicity (Schaake-Koning et al, 1992; Furose et al, 1999).

Postoperative radiotherapy

Previously, following resection of early stage disease, radiotherapy was used on the basis that it would eradicate microscopic disease at the resection margins. However, a meta-analysis published in 1998 demonstrated a significant adverse effect of postoperative radiotherapy (PORT) on survival of patients with stage I or II disease and is therefore no longer routinely used (PORT Meta-Analysis Trialists Group, 1998). This effect was not seen for patients with stage III N2 disease. Further research will be required to determine whether PORT will be of benefit to this group.

Radiotherapy in limited stage SCLC

Thoracic radiotherapy to consolidate chemotherapy and also prophylactic cranial irradiation are both now standard treatments in limited stage SCLC. They are used with different intentions but have both been proven to have a beneficial effect on survival and the benefits appear to be independent and additive.

Complete response rates of up to 90% can be achieved with chemotherapy and consolidation thoracic radiotherapy. Three-year survival has been increased by approximately 5% with the addition of radiotherapy as a result of the reduction in the rate of local relapse (Pignon et al, 1992). There remain unresolved issues, which are the subject of ongoing clinical trials; such as the optimal dose and timing of radiotherapy and whether fields should encompass pre-chemotherapy disease (at the expense of irradiating larger lung volumes). It is of little surprise that the greatest benefits have been demonstrated in younger patients, of good PS with a complete radiological and clinical response to chemotherapy.

The reduction in local relapse resulting from thoracic radiotherapy inevitably led to brain metastasis becoming an increasingly important cause of treatment failure. The incidence of brain metastasis in patients with limited disease is up to 50%. It has been known for some time that prophylactic cranial irradiation reduces the incidence of brain metastasis. More recently, meta-analysis has also demonstrated a reduction in mortality similar to that of thoracic radiotherapy, i.e. a 5% increase in overall survival at 3 years (Auperin et al, 1999). Again, optimal dose and timing of treatment have not been precisely determined. There have been concerns regarding neuropsychological sequelae following prophylactic cranial irradiation, but the effects are difficult to separate from the consequences of other potentially neurotoxic treatments and the effect of metastasis itself. More recent trials attempting to prospectively assess cognitive function have not demonstrated an increased risk of neuropsychological complications associated with prophylactic cranial irradiation.

PALLIATIVE RADIOTHERAPY

Radiotherapy is useful in achieving both rapid and effective control of local symptoms, particularly haemoptysis and pain. During the course of their disease, approximately half to one third of patients with lung cancer will receive palliative radiotherapy at some stage.

The literature reports a wide range of doses and fractionation schedules used for palliation (Macbeth et al, 2001). All studies appear to report improvement in symptoms following radiotherapy and higher doses are consistently associated with more acute side effects, particularly oesophagitis, tiredness and anorexia. As survival has only been shown to be influenced in a small minority of patients of good PS, it is preferable for the majority to use short, hypofractionated regimens, such as 10 Gy in a single fraction. This enables patients to be treated with a minimum number of visits to the hospital and also enables a reasonable throughput in the overstretched radiotherapy department. It is important to remember that radiotherapy is not only of use in the treatment of thoracic symptoms associated with lung cancer, but is also often the most effective way of managing other problems such as bone metastases and spinal cord compression. Endobronchial radiotherapy (i.e. brachytherapy) using high dose indium can produce useful relief of symptoms from bronchial obstruction at a single treatment session.

CONCLUSIONS

To date, the major treatment modalities for inoperable bronchial carcinoma have been chemotherapy and radiotherapy. Their roles have evolved and in particular have become integrated with each other and also with new and alternative treatment strategies. Despite the poor outlook for the majority of patients with incurable disease and the nihilism that this breeds, there have been appreciable improvements in both cure rates and quality of life. In the future these well-established treatments should be explored further as well as developing promising strategies such as molecular targeted therapy. Chemotherapy and radiotherapy are likely to remain pivotal to the treatment of this important condition. HM

Conflict of interest: none.

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KEY POINTS

- Bronchial carcinoma is the commonest malignant disease within the UK and is a major cause of morbidity and mortality.
- Chemotherapy and radiotherapy remain the major modalities of treatment.
- Small cell lung cancer is highly chemosensitive, but long-term survival is uncommon. Response rates and survival have been improved by the appropriate addition of thoracic radiotherapy and prophylactic cranial irradiation.
- Surgery or radical radiotherapy may be curative for early stage non-small cell lung cancer. The value of neoadjuvant chemotherapy is being explored.
- Palliative chemotherapy and radiotherapy may greatly improve quality of life and modestly improve survival in all forms of lung cancer.
- All patients with lung cancer should be referred to a specialist for consideration of treatment and should have their management discussed at a multidisciplinary meeting.