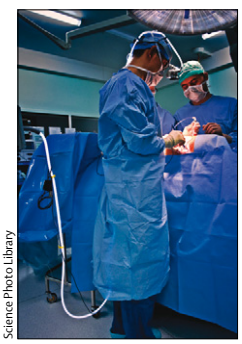
Improving rates of surgery for lung cancer



Science Photo Library

See **Seminar** pages 1727 and 1741

As two Seminars in this week's issue show, surgery has an important part to play in the management of early-stage lung cancer. Surgical lung resection offers good rates of cure for patients who have stage I or II non-small-cell lung cancer and immediate surgery is beneficial for those with small-cell lung cancer with very limited stage disease.

In the past, the UK's surgical resection rates have remained lower than those achieved in Europe and the USA, but a new audit suggests that this situation is changing. The UK's second *National Thoracic Surgery Activity and Outcomes Report* shows that the number of patients with lung cancer undergoing surgery has increased by 60% in the past 4 years, while post operative mortality has halved during the past decade from 3·8% to 2·1%.

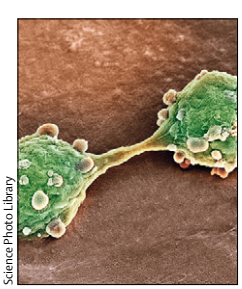
This improvement has been due in part to thoracic surgery becoming more defined as a specialty (as opposed to cardiothoracic surgery), resulting in an increase in surgeons in this area. However, there is still a need to boost numbers. The audit notes that, if the rate of operations across the country matched the best performing areas, then at least an additional 1000 lives could be saved each year. Furthermore, current evidence supports the expansion of surgery as part of multimodality management of patients with N2 disease (metastasis in ipsilateral mediastinal or subcarinal lymph nodes or both), and, as diagnostic techniques improve, more cancers will be detected at an operable stage.

Training in new surgical techniques also needs attention. Technical advances have led to the development of lung resection with video-assisted thoracoscopic access (VATS lung resection). In their Seminar on non-small-cell lung cancer, Peter Goldstraw and colleagues report no difference in mortality or local recurrence between open resections or VATS, but lower systemic recurrences and improved 5-year survival with VATS. The current balance of risks and benefits suggest that VATS might be a viable option for selected patients with early-stage lung cancer. Yet the national audit shows that only 35% of operations are done with VATS.

Further development of thoracic surgery as a specialty should be encouraged to improve the management of lung cancer in the future. ■ *The Lancet*

For **the UK audit** see http://www.scts.org/_userfiles/resources/63455886 9917493937_Thoracic _2011_FINAL.pdf

Moving toward precision medicine



Science Photo Library

The century-old International Classification of Diseases (ICD) is well known to epidemiologists and public health specialists, but little used in other areas of clinical research. New insights into human disease are emerging from basic research, and this explosion of information has the potential to revolutionise disease diagnosis, therapeutics, and clinical decision-making. Is a new taxonomy of human disease based on molecular and cell biology needed?

Toward precision medicine was released by the US National Research Council on Nov 2. Precision medicine would define diseases by underlying molecular causes and other factors in addition to traditional signs and symptoms. Moreover, a new data network could aid biomedical research by enabling access to information and tissue samples from patients. This approach would unify molecular and clinical research at the point of care.

A new disease taxonomy would be combined with an information bank, consisting of data for large patient populations available for research use, and a knowledge network, which would integrate information about causal factors of disease and allow researchers and the public to share and update information. The report makes six recommendations. First, pilot studies are needed to add data to information banks. Second, data need to be integrated to construct a disease knowledge network. Third, privacy issues need to be assessed. Fourth, data sharing needs to be ensured. Fifth, an efficient validation process needs to be developed. Finally, incentives should be established for research partnerships.

The precision medicine initiative could be worthwhile if it aids the development of targeted therapeutic agents and improves clinical outcomes. Yet establishment of access to very large sets of health and disease-related data linked to individual patients will involve profound cultural change, as well as raising difficult issues in ethics and data management. In addition to weighing the cost of such an initiative and how success will be judged, an assessment by the US Presidential Commission for the Study of Bioethical Issues might add valuable insight into the moral dimensions of this important work. ■ *The Lancet*

For the **report *Toward precision medicine*** see http://dels.nas.edu/Report/Toward-Precision-Medicine-Building-Knowledge/13284

Small-cell lung cancer

Jan P van Meerbeeck, Dean A Fennell, Dirk K M De Ruysscher

The incidence and mortality of small-cell lung cancer worldwide make this disease a notable health-care issue. Diagnosis relies on histology, with the use of immunohistochemical studies to confirm difficult cases. Typical patients are men older than 70 years who are current or past heavy smokers and who have pulmonary and cardiovascular comorbidities. Patients often present with rapid-onset symptoms due to local intrathoracic tumour growth, extrapulmonary distant spread, paraneoplastic syndromes, or a combination of these features. Staging aims ultimately to define disease as metastatic or non-metastatic. Combination chemotherapy, generally platinum-based plus etoposide or irinotecan, is the mainstay first-line treatment for metastatic small-cell lung cancer. For non-metastatic disease, evidence supports early concurrent thoracic radiotherapy. Prophylactic cranial irradiation should be considered for patients with or without metastases whose disease does not progress after induction chemotherapy and radiotherapy. Despite high initial response rates, most patients eventually relapse. Except for topotecan, few treatment options then remain. Signalling pathways have been identified that might yield new drug targets.

Lancet 2011; 378: 1741–55

Published Online
May 11, 2011
DOI:10.1016/S0140-6736(11)60165-7

See Editorial page 1678

Department of Respiratory Medicine and Lung Oncological Network, Ghent University Hospital, Ghent, Belgium (Prof J P van Meerbeeck CMO); **Belfast Cancer Research UK Centre, Queen's University Belfast, Belfast, UK** (D A Fennell FRCP); **and Department of Radiation Oncology (Maastro Clinic), Maastricht University Medical Centre, GROW—School for Oncology and Developmental Biology, Maastricht, Netherlands** (Prof D K M De Ruysscher MD)

Correspondence to:
Prof Jan P van Meerbeeck, Department of Respiratory Medicine and Lung Oncological Network Ghent University Hospital (LONG), De Pintelaan 185, B-9000 Ghent, Belgium
jan.vanmeerbeeck@ugent.be

Introduction

Small-cell lung cancer (SCLC) is a distinct clinical and histological entity within the range of lung cancers. Its management has followed the major developments of modern cancer treatment through the integration of biology, imaging, chemotherapy, and radiotherapy.

SCLC was originally thought to originate from the lymphatic system because of microscopic similarities between SCLC and lymphoma cells. In 1879, Härting and Hesse[1] described an arsenic-induced lymphosarcoma in miners. The term SCLC was first coined in 1926, when its epithelial origin was recognised.[2] In this and ensuing classifications, phenotypical variants were described as oat cell or mixed subtypes. These terms are no longer used in WHO's classification.[3]

Here we address the scientific advances that have been made in defining the biology of SCLC and that have increased our ability to manage this cancer. We also consolidate the evidence on the usefulness of current therapeutic and prophylactic methods, and suggest ways they can be further improved by new developments in targeted therapy.

Epidemiology

Lung cancer accounts for 12% of all new cases of cancers worldwide, it is the second most common cancer in men and women, and it is the leading cause of cancer-related death in the USA.[4] SCLC represents 13% of all newly diagnosed cases of lung cancer worldwide, or more than 180 000 cases per year. More than 90% of patients with SCLC are elderly current or past heavy smokers, and risk rises with increasing duration and intensity of smoking.[5] Although rare cases have been reported in people who have never smoked,[6] SCLC, by contrast with non-small-cell lung cancer (NSCLC), is not associated with a specific somatic mutation.[7] In industrialised countries the annual incidence of SCLC has decreased over the past 30 years, probably owing to changes in smoking patterns. A shift in the WHO classification of lung cancers might also have contributed, as some borderline cases that were previously described as mixed subtypes are now classified as NSCLC.[3,8] An increase in incidence is expected in countries where smoking prevalence remains high, such as those in eastern Europe and Asia.

Diagnosis

SCLC is defined as "a malignant epithelial tumour consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli" (figure 1).[3] Typical SCLC involves only small cells and accounts for around 90% of cases. The remaining cases are classified as combined disease, in which the tumour contains large-cell components.[3,9]

Molecular biology

Cytogenetically, SCLC has several distinguishing abnormalities in DNA copy number. In virtually all expression microarray analyses, SCLC has shown many specific gene expression features.[10] Several important genetic and molecular characteristics have been recorded, including the identification of autocrine growth loops, proto-oncogene activation, and loss or

Search strategy and selection criteria

We searched PubMed with the following keywords used in various combinations: "carcinoma", "small cell lung", "epidemiology", "pathology", "biology", "diagnosis", "staging", "treatment", "management", "antineoplastic agents", "targeted agent", "radiotherapy", and "surgery". The search was limited to articles published in peer-reviewed, journals published from 2005 onwards. For the management section we searched all publications and for the other sections we only searched journals published in English. Some classic papers were also selected according to the authors' knowledge. We consulted the latest guidelines of the National Institute for Health and Clinical Excellence in the UK, the American College of Chest Physicians, the National Comprehensive Cancer Network, and the European Society of Medical Oncology.

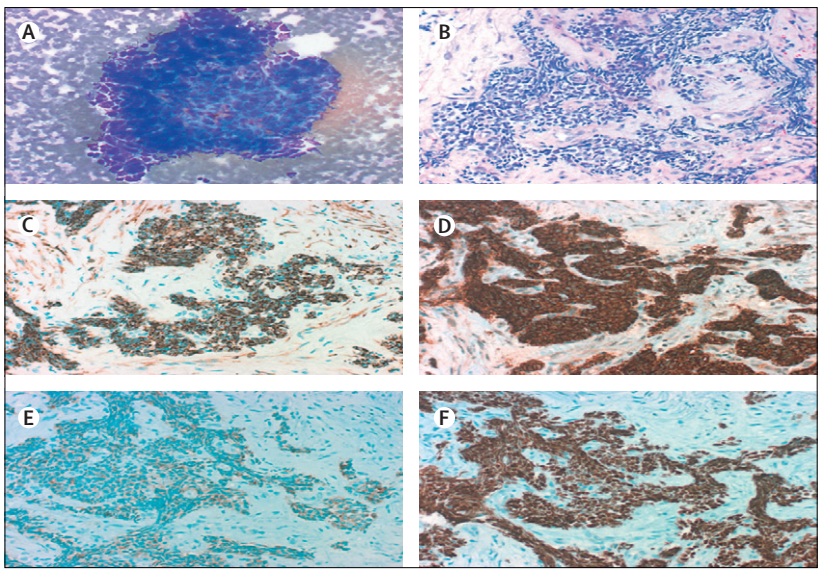


Figure 1: **Microscopic features of SCLC**
(A) In typical SCLC, cells are small (generally less than the size of three small resting lymphocytes) with scant cytoplasm, nuclear moulding, and finely granular nuclei with inconspicuous nucleoli (Diff-Quick staining, ×200). (B) Cells can be round, oval, or spindle-shaped and cell borders are rarely seen. Architectural patterns include nesting, trabeculae, peripheral palisading, and rosette formation, as seen in other neuroendocrine-tumour cells (haematoxylin and eosin staining, ×200). Immunohistochemistry shows strongly positive results for (C) CK-7, the neuroendocrine markers (D) CD56 and (E) synaptophysin, and (F) TTF-1 along plasma membranes and in the nuclei. SCLC=small-cell lung cancer. All pictures reproduced by permission of M Praet and L Ferdinande, N Goormaghtigh Institute of Pathology, Ghent, Belgium.

inactivation of tumour-suppressor genes.[9] The deletion 3p(14–23) in the region containing the tumour-suppressor gene *FHIT* is seen in virtually all SCLC tumours.[9] Another common finding is a copy-number gain in 7p22.3, which encompasses *MAD1L1*, which encodes the mitotic spindle assembly checkpoint protein MAD1.[11] Nearly all patients with SCLC also have loss of the tumour-suppressor retinoblastoma gene *RB1* and have more frequent mutations in *TP53* than do patients with NSCLC. These mutations decrease proapoptotic activity during SCLC tumorigenesis, which encourages agressive growth and increases the survival advantage of carcinogenic cells.[12] Tyrosine-kinase signalling genes, including *KRAS* and *EGFR*, are rarely mutated.[9] Information on the molecular features of SCLC is, however, not yet sufficient to affect diagnostic methods.

Histopathology

Although SCLC is often suspected on the basis of presenting symptoms and signs, pathological and cytopathological studies are typically required to confirm the diagnosis. Samples from the primary tumour, lymph nodes, or other metastatic sites should be obtained by bronchoscopic biopsy or fine-needle aspiration. The tumour grows under the bronchial mucosa and, therefore, bronchial biopsy, cytological brush, or sputum samples might be negative. Necrosis or crush artifacts by the bronchoscopic forceps sometimes hamper diagnosis, but good interobserver agreement has been reported between pathologists for differentiation of SCLC from NSCLC.[3,9] Immunohistochemical studies can be used to confirm difficult cases. Testing for neuroendocrine markers, such as chromogranin, synaptophysin, and CD56, can be useful (figure 1); less than 10% of SCLC tumours are negative for all neuroendocrine markers. SCLC is also positive for TTF-1 in up to 90% of cases. Epithelial markers, such as cytokeratins, are seen in many SCLC tumours and help to distinguish them from lymphomas and other small round tumours.

Presentation

Watson and Berg[13] were the first to describe distinct clinical features of SCLC, especially the predominantly central and bulky location on chest radiography, the tendency for early dissemination, the high initial response rates to chemotherapy, and the high frequency of metastases at autopsy. Patients are typically men older than 70 years who are heavy current or ex-smokers and have various pulmonary, cardiovascular, and metabolic comorbidities.[14] Onset of symptoms is rapid, with the duration before presentation generally being 8–12 weeks. The most frequent symptoms are cough, wheeze, dyspnoea, haemoptysis caused by local intrapulmonary tumour growth, symptoms due to intrathoracic spread to the chest wall, superior vena cava, or oesophagus, recurrent nerve, pain, fatigue, anorexia, and neurological complaints caused by distant spread, and paraneoplastic syndromes.[15,16] Preferential metastatic sites are the brain, liver, adrenal glands, bone, and bone marrow.

SCLC is the most frequent cause of paraneoplastic syndromes (table 1).[28] These syndromes should be actively excluded whenever a patient presents with any of their associated features. The most frequent endocrine syndromes are the syndrome of inappropriate anti-diuresis[17,18] and Cushing's syndrome.[19,20] Subclinical presentations of both have been reported. Dermatological abnormalities specifically associated with SCLC include acquired tylosis, trip palms, and erythema gyratum repens.[15]

Rarer manifestations are dermatomyositis, hyperglycaemia, hypoglycaemia, hypercalcaemia, and gynaecomastia. SCLC elicits various serum antibody responses. Among these, neurological syndromes are of special interest, owing to the generation of autoantibodies and T lymphocytes specific for common epitopes in the tumour and components of the nervous system.[21] These syndromes can antedate a diagnosis of SCLC by several months. Lambert-Eaton syndrome is a disease of the neuromuscular junction and is caused by antibodies directed against the P/Q-type voltage-gated calcium channels in the presynaptic nerve terminal that are expressed by SCLC cells. This complication suggests autoimmunisation by the tumour is the cause of the

	Main symptoms, signs, and findings	Cause	Proportion of SCLC patients with syndrome (%)	Proportion of patients with the syndrome that have SCLC (%)	Prognosis
Syndrome of inappropriate antidiuresis[17,18]	Weakness, dysgeusia, and clinical euvolaemia (osmolality <275 mOsmol/kg water, urinary osmolality >100 mOsmol/kg water during hypotonicity, urinary sodium >40 mmol/L with normal dietary salt intake)	Arginine vasopressin or atrial natriuretic peptide	15–40	..	Frequently normalises with treatment but precedes relapse
Cushing's syndrome[19,20]	Hypercorticism	Ectopic corticotropin	2–5	3–11	Poor owing to high rate of infections during chemotherapy
Lambert-Eaton syndrome[21–24]	Muscle weakness and fatiguability, mostly in proximal muscles of lower extremities, abnormal gait, hyporeflexia, increased deep-tendon reflexes after facilitation, autonomic dysfunction, and paraesthesia	Antibodies to voltage-gated calcium channels of nerve terminal and to SOX	3	50	50% of patients improve during treatment, 50% refractory
Limbic encephalitis and encephalomyelitis[21,25–27]	Personality and psychiatric changes, seizures, short-term memory loss, and space and time disorientation, with or without dementia	Antibodies to Hu family proteins	<1	50	Neurological symptoms not reversible
Paraneoplastic cerebellar degeneration or Hu syndrome[21,25–27]	Truncal, limb, and gait ataxia, dysarthria; ocular findings, and vertigo with inability to stand, walk, or sit	Antibodies to Hu family proteins, YO, CRMP-5, Pca-2, MA1, voltage-gated calcium channels of nerve terminal, and RI	<1	5	Neurological symptoms not reversible
Superior vena cava syndrome[16]	Oedema of upper body	Obstruction of superior vena cava by primary tumour, enlarged mediastinal lymph nodes, or thrombus	50	25	Resolves rapidly with chemotherapy or radiotherapy

SCLC=small-cell lung cancer.

***Table 1*: Paraneoplastic and other syndromes frequently associated with SCLC**

	Number of patients	Origin of patients' details	Factors associated with improved outcomes		
			Patient	Tumour	Biology
Cerny et al[35]	407	Manchester Group clinical trials	Karnofsky performance status >80	Limited stage	Normal baseline concentrations of LDH, sodium, alkaline phosphatase, or bicarbonate in serum
Albain et al[36]	1137	SWOG clinical trials	Age <70 years	Limited stage, no pleural effusion	Normal baseline concentration of LDH in serum
Sagman et al[37]	614	Clinical trials	ECOG performance status 0–1; female sex	Limited stage, no liver metastasis	Normal baseline concentrations of LDH or alkaline phosphatises in serum or normal baseline WBCC
Paesmans et al[38]	763	ELCWP clinical trials	Karnofsky performance status >80; female sex; age <60 years	Limited stage	Baseline neutrophil rate <75%
Sculier et al[39]	4359	IASLC database	Performance score <1, female sex, age <65 years	Limited stage	..
Foster et al[40]	910 (ES only)	NCCTG clinical trials	Performance status <1, female sex	Low number of metastatic sites	Normal baseline creatinine concentration

SCLC=small-cell lung cancer. LDH=lactate dehydrogenase. SWOG=South West Oncology Group. ECOG=Eastern Cooperative Oncology Group. WBCC=white-blood-cell count. ELCWP=European Lung Cancer Working Party. IASLC=International Association for the Study of Lung Cancer. ES=extensive stage SCLC. NCCTG=North Central Cancer Treatment Group Trials.

***Table 2*: Prognostic factors in reported in SCLC database studies**

syndrome. In one series, five of 63 unselected SCLC patients had raised concentrations in serum of antibodies against P/Q-type voltage-gated calcium channels, although only two had Lambert-Eaton syndrome.[22] Antibodies against SOX family proteins have diagnostic value in discriminating Lambert-Eaton syndrome associated with SCLC from other non-tumorous forms.[29] Lambert-Eaton syndrome should be differentiated from myasthenia gravis, which is not frequently associated with SCLC.

Patients with SCLC might have raised concentrations of antibodies against other antigens, such as the Hu family of DNA-binding proteins. Paraneoplastic encephalomyelitis and paraneoplastic sensory neuronopathy have been associated with raised titres of antibodies to Hu family proteins.[25] Low titres in serum,

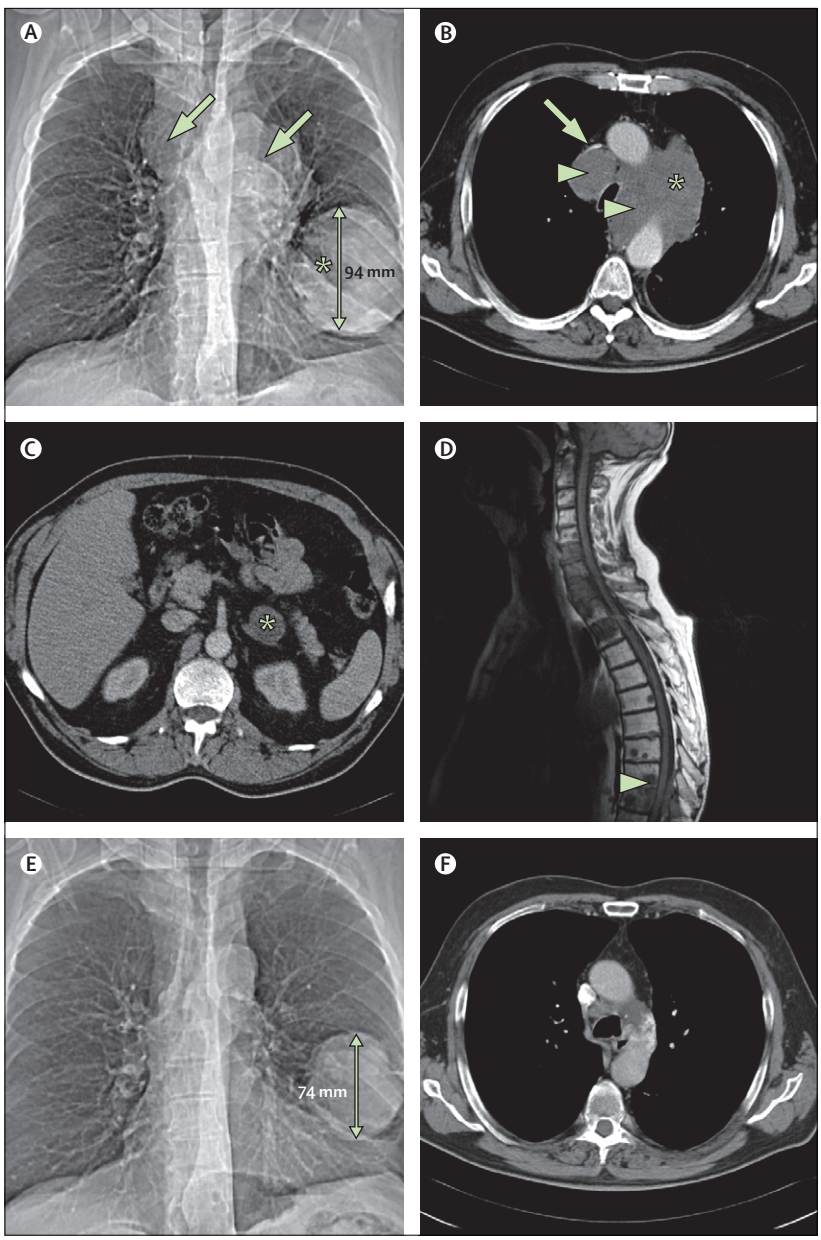


Figure 2: **Radiological imaging of SCLC at presentation and after treatment in a patient presenting with dyspnoea, stridor, and superior vena cava syndrome**
(A) Radiography showed a left lower lobe tumour (asterisk) with multiple enlarged mediastinal lymph nodes (arrows). (B) On CT the superior caval vein and the trachea were compressed (arrow), multiple lymph nodes were enlarged in the para-aortic (asterisk) and both paratracheal zones (arrowheads), and (C) left adrenal metastasis could be seen (asterisk). (D) MRI showed diffuse vertebral metastases with medullar compression at the level of T9–T10 (arrowhead). After two cycles of etoposide and cisplatin a partial response was seen (E) on radiography and (F) on CT, with shrinkage of 20% in the primary tumour and reduction in size of the mediastinal lymph nodes.

without accompanying clinical paraneoplastic syndrome, have been found in 16% of neurologically asymptomatic patients with SCLC.[30]

Staging and prognosis

The aggressive early locoregional and distant spread of SCLC led the Veterans Administration Lung Study Group, in 1957, to create a dichotomised staging system: limited stage was characterised by a tumour volume encompassed in one radiation portal; all other disease spread was classified as extensive stage.[31] 50 years later, the International Association for the Study of Lung Cancer recommended that the TNM classification system should be used for SCLC as well as for NSCLC.[32] This recommendation was based on a retrospective analysis of data from 8000 patients with SCLC, which showed significantly worse survival for patients with limited-stage disease and mediastinal lymph node involvement (TNM stage III) than for those with no lymph node involvement (stage I) or with N1 lymph node involvement (stage II).[33] Intermediate prognosis was assigned to patients with pleural effusion, between that for patients in stage III and those with haematogenous spread (stage IV). Thus, patients with cytologically negative effusions are now classified as having stage III disease. Although its simplicity makes the Veterans Administration Lung Study Group classification attractive for use in routine practice, clinicians and cancer registrars are nevertheless strongly encouraged to use TNM staging. This classification can be easily converted to limited stage (TNM stages I–III) and extensive stage (TNM stage IV).

Prognosis in SCLC is poor. Median survival without treatment has been reported as 2–4 months.[34] The most reproducible prognostic factor is disease extent, although a few other prognostic factors have been identified: performance status, sex, and some routine laboratory tests show some merit.[35–40] No histological or molecular features are prognostically useful.[41] Several algorithms have been validated for predicting survival (table 2).[35–40] The individual value of these tools, however, remains poor.[42] Paraneoplastic syndromes are more frequently seen in patients with limited-stage SCLC than in those with extensive-stage disease, but their presence is not unequivocally prognostically favourable (table 1).[23,24,26,27]

As disease extent is the major prognostic factor, staging aims to identify whether the tumour has metastasised (figure 2). The number and sequence of staging tests should be guided by the patient's signs and symptoms at presentation, the most likely sites of metastatic involvement at diagnosis, and the availability and accuracy of the diagnostic tests. Around two-thirds of patients present with clinically obvious metastatic disease, although unequivocal proof can be challenging. Even in patients whose history and clinical examination suggest that disease is limited to the hemithorax, a full assessment should be planned because identification of occult dissemination spares patients from unnecessary chest radiotherapy.

In view of the rapid growth of SCLC tumours, staging should be done quickly and include at least full history, physical examination, chest radiography, complete blood count (including differential counts), liver and renal

function tests, assay of lactate dehydrogenase and sodium concentrations, and contrast-enhanced CT of the chest and upper abdomen. Bone scintigraphy is optional. CT or MRI of the brain with intravenous contrast are recommended in patients being considered for chemoradiation with curative intent,[43] or are mandatory[44,45] to exclude asymptomatic brain metastases. In one series, the prevalence of brain metastases was 10% with CT and 24% with MRI.[46] All CT-detected brain metastases were symptomatic, whereas 11% of those detected by MRI were asymptomatic. Bone-marrow infiltration should be suspected if an isolated rise in lactate dehydrogenase concentration or blood counts indicating otherwise unexplained anaemia or a leucoerythroblastic response are seen.

Once metastatic spread is detected by one test, further staging can be omitted in the absence of symptoms that require intervention. Routine use of pulmonary function tests is not necessary, other than to exclude or assess comorbid pulmonary disease.[47] Use of combined fluorodeoxyglucose PET (FDG-PET) and CT notably improves the accuracy of staging in NSCLC by the detection of mediastinal nodal and occult metastatic spread, but its routine use in SCLC remains controversial. PET is, however, being used for fast-track diagnosis or to plan radiotherapy in some countries. Evidence that it changes the planning target volume is limited,[48] and wider implementation will probably increase the proportion of patients who are identified as having metastatic patients, which could improve stage-specific survival because of stage migration.[49] Most chemoradiation trials were done, however, before PET was available.

Management

Early treatments for SCLC were nitrogen mustard,[50] surgery (which was first used in 1948), radical radiotherapy,[51] and cyclophosphamide; treatment with cyclophosphamide significantly favoured survival.[52] In the mid-1970s, the possibility of cure seemed feasible as new drugs were developed and combination chemotherapy became possible and led to better results than did single-agent treatments.[53] Although no cure has emerged, combined chemotherapy remains the cornerstone for all stages of SCLC.[54] Median survival for patients with limited-stage disease is currently 15–20 months, with 20–40% surviving to 2 years, and for those with extensive-stage disease the values are 8–13 months and 5%, respectively.[55] Since the mid-1980s, increases in survival have slowed[56] although stage migration, platinum-based chemotherapy, and radiotherapy have all exerted beneficial effects. A simplified treatment algorithm of SCLC is given in figure 3.

Identification of the best drug combinations and scheduling have been the focus of much investigation for the past 30 years. Anthracycline-based treatment in combination with cyclophosphamide and vincristine

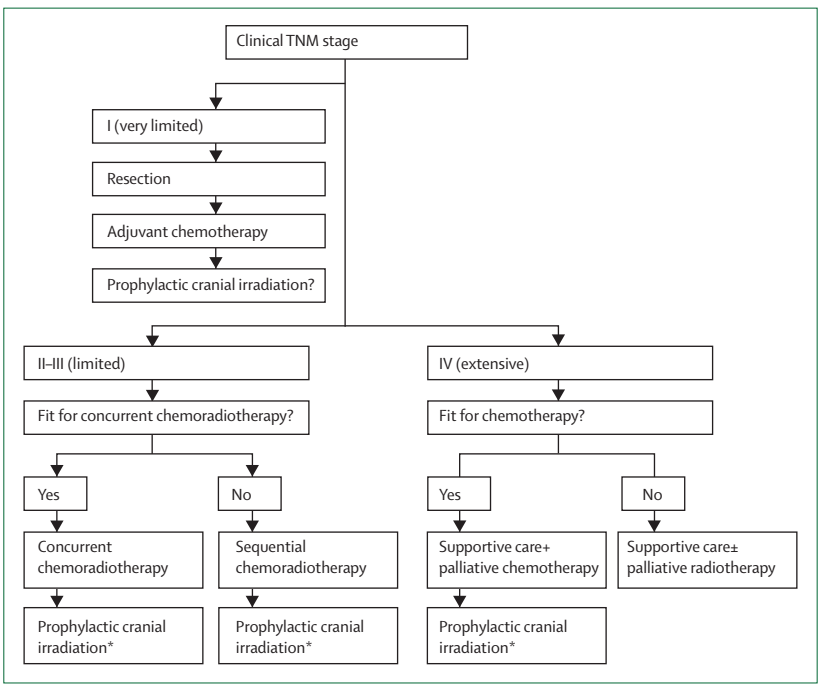


***Figure 3*: Simplified algorithm for the management of SCLC**
SCLC=small-cell lung cancer. *If not progressive after induction treatment

became standard therapy during the 1970s,[57] followed by etoposide-containing regimens,[58] Cisplatin-based regimens became first-line treatment in the 1980s.[59,60]

Extensive-stage disease

SCLC is very chemosensitive and, therefore, chemotherapy can produce rapid responses with sometimes striking improvements in symptoms and outcomes. First-line treatment is also useful in patients with poor performance status,[61] by contrast with the situation in NSCLC, albeit at the risk of serious toxic effects.

The first-line treatment of choice in extensive-stage SCLC remains four to six cycles of etoposide combined with a platinum salt (cisplatin or carboplatin). In two meta-analyses such a combination was better than other combined treatments,[62,63] although a third analysis did not support the findings (table 3).[64] Differences in design probably explain the discrepancy. All three analyses included patients with extensive-stage and limited-stage disease, but one did not include trials involving any regimen containing carboplatin,[62] and in another the study regimens had to include etoposide, cisplatin, or both, and the same drug or drugs had to be omitted from the control groups.[63] The third meta-analysis included trials comparing any platinum agent at any dose or for any number of cycles compared with any other chemotherapy regimen.[64] The substitution of cisplatin by carboplatin to avoid the side-effects of cisplatin is unlikely, however, to have contributed to the discrepancy between the meta-analyses because survival was not

	Regimens	Number of trials/patients	Response	Outcome	Toxic effects
Pujol et al[62]	Etoposide and cisplatin *vs* non-platinum-based-chemotherapy*	19/4054	Increased response rate with cisplatin (OR 1·35, 95% CI 1·18–1·55; $p<1\times10^{-5}$)	Reduced risk of death at 1 year (OR 0·80 [95% CI 0·69–0·93], p<0·002)	No difference in mortality related to toxic effects
Mascaux et al[63]	Etoposide, cisplatin, or both *vs* one or neither drug	36/7173	NR	Survival benefit in favour of etoposide alone or in combination with cisplatin	NR
Amarasena et al[64]	Platinum-based *vs* non-platinum-based	29/5530	Significantly higher rate of complete response with platinum-based regimen, no significant difference in overall tumour response	No significant difference in survival at 6, 12, and 24 months; risk ratios numerically favour platinum-based regimens	Significantly higher rates of nausea, vomiting, anaemia, and thrombocytopenia with platinum-based regimen

SCLC=small-cell lung cancer. OR=odds ratio. NR=not reported. *Etoposide was administered in some comparison groups.

***Table 3*: Meta-analyses of platinum-based compared with non-platinum-based chemotherapy in SCLC**

altered, even with the use of split doses of both drugs in elderly patients or those with poor outlook.[65] Many clinicians already deem carboplatin to be an acceptable palliative option for extensive-stage SCLC when the tolerability of full-dose etoposide with cisplatin is of concern.[43] In one review toxic effects were increased with regimens containing platinum,[64] although the effects on quality of life could not be assessed because of a lack of data. Major differences in quality-of-life outcomes between an anthracycline and platinum-based regimen are, however, not expected, and use of modern antiemetics and growth factor transfusions will probably be able to counteract these toxic effects. Large comparative studies of quality of life are, therefore, unlikely to be done in the near future.

In a pooled meta-analysis of six trials involving 1476 previously untreated Asian and white patients with extensive-stage SCLC, irinotecan and platinum combination regimens were associated with higher response rates and better overall survival than was etoposide and cisplatin.[66] The irinotecan-containing regimens led to less severe anaemia, neutropenia, and thrombocytopenia but more severe vomiting and diarrhoea than those containing etoposide and cisplatin; treatment-related mortality was similar. Whether the results of this meta-analysis apply to white patients is debatable, as rates of toxic effects and death have been lower in Asian than in European or US trials.[67–70] Differences between Japanese and white patients in the frequency of variant alleles that encode topoisomerase I enzymes, which are involved in DNA repair and affect irinotecan metabolism, might explain this discrepancy.[71] Amrubicin is a synthetic anthracycline that inhibits topoisomerase I and has shown promising first-line activity when used alone or in combination with platinum,[72] and might provide an alternative to irinotecan. Thus, in patients with extensive-stage SCLC who are otherwise fit, four to six cycles of etoposide and cisplatin (in non-Asian patients) or irinotecan and cisplatin (in Asian patients) should result in a complete response rate of more than 20% and keep treatment-related mortality below 5%.

Strategies that have alternated non-cross-resistant drugs and increased total dose, dose intensity, number of courses, or number of drugs have been unsuccessful. These approaches are not recommended outside clinical trials.[73]

Preliminary evidence suggests that adding thoracic radiotherapy to chemotherapy improves survival in patients with extensive-stage SCLC who have a complete response outside the thorax and at least a partial response within the thorax after three cycles of etoposide and cisplatin.[74] This finding, however, was from a single-centre trial, and the results of a larger, multicentre Dutch randomised trial (CREST) and a US trial (NCT01055197) are awaited.

Immediate whole-brain radiotherapy is indicated in patients with brain metastases and intracranial hypertension, pending lock-in syndrome, or other neurological emergencies. In some series in patients with SCLC and NSCLC and brain metastases whole-brain radiotherapy combined with different chemotherapy regimens seemed to increase the risk of neurological toxic effects, but also to increase response rates and lengthen the time to progression of brain metastasis.[75–78] This increase in toxic effects was probably related to the use of anthracyclines and high doses of radiation per fraction. On the basis of this evidence whole-brain radiotherapy should be started after the completion of chemotherapy in patients with brain metastases, with or without symptoms, but not delivered concomitantly with cytotoxic treatment.

Limited-stage disease

Although SCLC is deemed a systemic disease, local treatments might have a role in certain patients with limited-stage disease. Immediate surgery should be considered for individuals who have biopsy-proven T1N0M0 tumours, but only after node negativity has been

confirmed by endoscopic ultrasonographic or mediastinoscopic staging. These patients typically present with a pulmonary nodule, the nature of which can only be ascertained after resection. The role of postinduction surgery has never been greatly explored because most patients with non-metastatic SCLC present with unresectable stage III tumours. Two phase 3 trials of surgery alone or in combination with chest radiotherapy showed no survival advantage compared with radiotherapy alone.[51,79] A review of the data from these studies, however, suggests that the usefulness of surgery was underestimated because resection was not complete in all patients assigned surgery.[51,79] Retrospective reports suggest that surgery led to good local control and favourable long-term survival in highly selected patients with stage I–III SCLC.[80,81] A formal randomised trial, however, has never started.[82] Adjuvant chemotherapy is recommended in patients who undergo surgery, followed by prophylactic cranial irradiation. This approach yields 5-year survival rates up to 57%.[41]

Meta-analyses indicate that chemotherapy combined with chest irradiation improves survival.[83,84] An improvement of around 5·4% in the absolute survival at 3 years was observed in patients who received chest radiotherapy after induction chemotherapy, compared with that in patients receiving chemotherapy alone. The 5-year survival rate, however, remained disappointingly low at 10–15%. Among chemotherapy regimens some had better effects than others. For instance, survival was significantly better in patients who received etoposide and cisplatin than among those given a cyclophosphamide, etoposide, and vincristine regimen.[60] In a small, randomised study, chest radiotherapy plus cisplatin instead of carboplatin, alone and in combination with etoposide, resulted in similar survival.[85] New drugs added to etoposide and cisplatin or tested as new regimens have not improved outcomes.[86–90]

Data on the optimum radiotherapy dose and fractionation come mostly from retrospective and phase 2 prospective studies. The results from non-randomised studies of patients receiving sequential or alternating schedules of chemotherapy and radiotherapy indicate a notable increase in local control when the dose is increased from 35 to 40 Gy and a possible slight further gain with 50 Gy.[91] Whether dose escalation to higher than 45–50 Gy is beneficial in patients receiving concurrent chemotherapy and radiotherapy, however, is unclear. The current standard regimen of a 45 Gy dose administered in 1·5 Gy fractions twice daily for 30 days is being compared with higher-dose regimens in two phase 3 trials, one in the USA (NCT00433563) and one in Europe (NCT00632853).

The definition of the target volumes is important to keep irradiation of normal tissues and side-effects to a minimum. In NSCLC, elective irradiation of the mediastinum has gradually been replaced by treatment limited to mediastinal nodes identified by CT or FDG-PET as being involved. Little evidence to support this approach in SCLC is, however, available. In a prospective study in which only CT-positive mediastinal lymph nodes in patients with limited-stage SCLC were included in the target volume, the isolated recurrence rate was 11%, which was higher than expected.[92] Irradiation of only nodes positive on FDG-PET was tested in a phase 2 study.[48] Among 60 patients isolated nodal failures were seen in only two (3%). Confirmation of this finding is awaited. Elective nodal irradiation, therefore, remains the recommended approach outside clinical studies.

Many phase 3 studies have been done to investigate the optimum timing of chest irradiation.[93,94] At 5 years, survival was significantly higher when chest radiotherapy was given within 30 days of starting platinum-based chemotherapy than when it was started after 30 days (20% *vs* 14%). In a pivotal phase 3 study, shortening the duration of radiotherapy also increased survival: 45 Gy administered in 1·8 Gy fractions once daily in 25 treatments over 5 weeks yielded 16% survival, compared with 26% after 1·5 Gy fractions twice daily for 3 weeks.[95] All patients received concurrent etoposide and cisplatin. Grade 3 acute esophagitis was reported in 56 (27%) of 211 patients who received accelerated radiotherapy and in 22 (11%) of 206 who received non-accelerated radiotherapy. In this trial, elective mediastinal radiotherapy was used. Importantly, toxic effects to the lungs did not differ between groups. A time interaction was suspected between chest irradiation and chemotherapy and, therefore, accelerated repopulation was postulated to be triggered by the first dose of any effective cytotoxic agent.[96] Thus, to obtain local tumour control, the last tumour clonogen should be killed by the end of radiotherapy. Long-term survival, therefore, decreases with increasing time between the start of any treatment to the end of radiotherapy (figure 4). A meta-analysis showed better long-term survival if time from the start to the end of radiotherapy was shorter than 30 days.[96] These results are consistent with the hypothesis that accelerated proliferation of tumour clonal cells is triggered by radiotherapy, chemotherapy, or both.

In summary, for limited-stage SCLC, current evidence supports early administration of 45 Gy with concurrent etoposide and cisplatin at systemic doses. If for reasons of fitness or availability this regimen cannot be offered, chest radiotherapy should follow induction chemotherapy.

Prophylactic cranial irradiation

The response rate and a median survival after whole-brain radiotherapy in SCLC patients with recurrence in the brain alone are 50% and 4–5 months, respectively.[97] Several randomised studies have been done, therefore, to investigate the usefulness of prophylactic cranial irradiation against microscopic brain involvement in limited-stage disease. Prophylactic cranial irradiation could indeed kill small tumour deposits with low

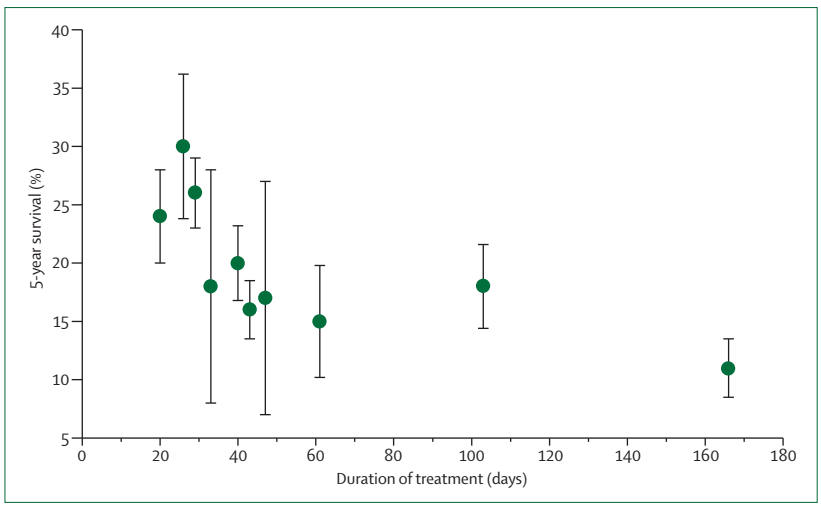


***Figure 4*: Survival at 5 years as a function of the time from the start of any treatment to the end of radiotherapy**
Each dot represents one trial with and error bars show SE. Reproduced from reference 96 by permission of the American Society of Clinical Oncology.

radiation doses, thus resulting in increased long-term survival if all extracranial cancer is controlled. In an update of a meta-analysis of studies involving patients in radiographically confirmed remission, the addition of prophylactic cranial irradiation was significantly associated with higher 3-year survival than no cranial irradiation (21% *vs* 15%, p=0·01).[98] Furthermore, disease-free survival was higher and cumulative incidence of subsequent brain metastases was lower for patients who received prophylactic cranial irradation. A significant trend was seen for effect on prevention of brain metastases, which seemed to increase with decreasing time between induction therapy and irradiation, although the relative risk of death was not altered.

Radiological assessment of response after radiotherapy is notoriously inaccurate because changes cannot be distinguished from active tumour.[91] In current phase 3 trials, therefore, patients without progressive disease are being offered prophylactic cranial irradiation (NCT00433453 and NCT00632853). After this meta-analysis a 25 Gy dose delivered in 2·5 Gy fractions once daily for 10 days became standard. In a large phase 3 trial, patients with limited-stage SCLC in remission after induction chemotherapy were randomly assigned this standard or a higher radiation dose of 36 Gy.[99] No survival benefit was seen with the higher dose and the risk of neurotoxic effects was increased.[100] On the basis of these results, this standard regimen remains recommended.

In patients with extensive-stage (stage IV) SCLC, symptomatic brain metastases occur in up to 50% and, therefore, the use of prophylactic cranial irradiation seems justified. In a phase 3 trial, patients who received prophylactic cranial irradiation had a lower risk of symptomatic brain metastases at 1 year than did controls (15% *vs* 41%) and 1-year survival was almost twice as high (27% *vs* 13%).[101]

Little investigation has been done into the neurotoxic effects of prophylactic cranial irradiation.[102–104] Neurocognitive testing before irradiation has shown impaired cognitive function in 47% of patients.[102–104] Some transient and early decline is seen in executive function and language performance after prophylactic cranial irradiation.[102–104] Large daily fractions and concomitant chemotherapy should be avoided. Furthermore, competing risk factors for neurocognitive decline (eg, mental stress, paraneoplastic syndromes, small-vessel CNS thrombosis, and age-related predisposition) should be carefully assessed before administration.[105]

Overall, prophylactic cranial irradiation should be planned for all patients with SCLC but no comorbidities and with no disease progression after induction therapy. Caution should be exercised when treating patients with severe medical comorbidities, poor performance status, or impaired neurocognitive function.

Relapsing and refractory disease

Despite high initial response rates, relapse is frequent after combined etoposide and cisplatin, probably because of rapid selection of a small number of residual tumour-insensitive cells or stem cells.[96] Patients are classified as having relapsed if disease returns after treatment. Patients are classified as being sensitive to treatment if recurrence is seen 90 days or more after the end of first-line treatment, or resistant if disease recurs within 90 days. If disease progresses during first-line treatment, SCLC is classified as refractory (figure 5). Only sensitive patients benefit from rechallenge with first-line treatment.

Second-line treatment is an option in only a few patients, owing to rapid disease progression and poor performance status. When used, the response rate is low and, although a significant benefit is seen, the duration of survival is only a few months longer than best supportive care.[106] Third-line treatment for SCLC is very rarely used.

Topotecan is currently the only approved drug for the treatment of patients with SCLC who relapse after first-line chemotherapy.[107,108] Administration of 1·5 mg/m² in 30 min infusions given daily for 5 days in cycles with 21 day intervals leads to outcomes similar to those achieved with a cyclophosphamide, doxorubicin, and vincristine regimen after first-line treatment with etoposide and cisplatin.[109]

Owing to the frequency of relapse, several new drugs have been assessed, including anthracyclines, camptothecins, antifolates, and taxanes.[73,110] A randomised, phase 2 trial of amrubicin compared with topotecan indicated efficacy of amrubicin in sensitive and resistant patients.[111] This drug is being assessed further in trials in first-line and second-line regimens (NCT00547651, NCT00388960, NCT00660504).

The efficacy of picoplatin, a platinum compound designed to overcome platinum resistance and toxic effects, is being investigated.[112,113]

Non-tumour treatment targets

Several targeted therapies have been assessed in SCLC, but, unlike for advanced-stage NSCLC, none has made their way into daily practice.[73,110,114] Various small-molecule inhibitors of different receptor tyrosine kinases (eg, EGFR, c-Kit, and VEGFR) have been studied in phase 2 trials, with or without chemotherapy, but did not show the expected activity, probably because patients were not selected according to target expression. Two large, randomised, phase 3 trials showed no significant benefits from adding thalidomide, a broadly targeted, antiangiogenic agent, to standard chemotherapy. Similarly, the addition of two different matrix metalloproteinase inhibitors to standard chemotherapy did not improve survival and adversely affected quality of life. A vaccine against the ganglioside family of antigens on the SCLC surface has shown no benefit.

Results with systemic treatments and therapies used to treat the symptoms of paraneoplastic syndromes have varied (table 1). Endocrine and dermatological abnormalities have often resolved, but neurological symptoms have generally remained refractory. Changes in concentrations of biochemical markers or antibodies can precede relapse.

Treatment with anticoagulants has been proposed for cancer owing to an antitumour effect. In a meta-analysis warfarin has been associated with lower mortality at 6 months in SCLC, particularly in patients with extensive-stage disease, but the risk of major and minor bleeding was increased and the advantage was not sustained at 1 year.[115] Heparin was associated with a survival benefit in cancer patients in general, and in particular in patients with limited-stage SCLC, but not in those with extensive-stage disease.[116] Randomised trials to investigate the use of low-molecular-weight heparins in SCLC are currently recruiting patients in Sweden (NCT00717938) and the UK (NCT00519805).

In preclinical studies, simvastatin suppressed tumour growth, induced apoptosis of SCLC cells, and increased tumour sensitivity to etoposide.[117] Pravastatin might stop the growth of tumour cells by blocking some of the enzymes needed for cell growth and increasing tumour cells sensitivity to chemotherapy.[118] A randomised, controlled, phase 3 trial to investigate the addition of pravastatin to standard first-line treatment in SCLC is currently accruing in the UK (NCT00433498).

Smoking cessation

Smoking cessation should be an integral part of the management of patients with SCLC. Patients who cannot quit alone should be referred for specialist help, such as in smoking clinics.[119] Tobacco smoke exacerbates oral mucositis and leads to loss of taste, xerostomia, weight loss, and fatigue.[120] Patients with lung cancer who stop smoking report decreases in fatigue and dyspnoea, and improvements in activity level, sleep, and mood.[121] Smoking during radiotherapy has been associated in some studies with an increase in the probability of radiation pneumonitis,[122] but not in others.[123] Finally, continuing or relapsing smokers are at increased risk of second primary tumours[124] and prognosis is poorer than that in patients who stop smoking altogether.[125]

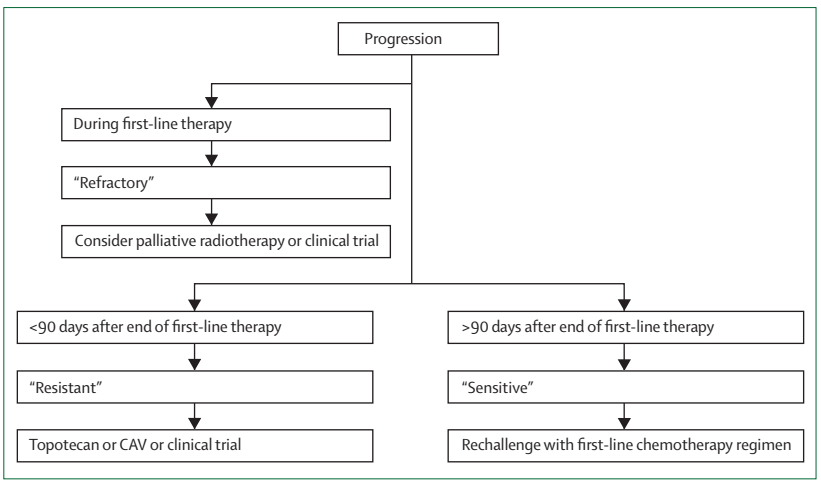


***Figure 5*: Simplified algorithm for the management of relapsing SCLC**
SCLC=small-cell lung cancer. CAV= cyclophosphamide, doxorubicin, and vincristine.

Novel biological targets

Evasion of apoptosis is a hallmark of cancer and is a major factor underlying drug resistance in SCLC. The mechanisms are complex and incompletely understood, but, similarly to other cancers, SCLC cells seem to suppress apoptosis by at least three mechanisms: increase in stimulation of antiapoptopic pathways via extracellular signals, desensitisation of the intrinsic cell death machinery via addiction to antiapoptosis proteins, and mutational burden leading to the loss of proapoptotic tumour suppressors. These mechanisms might offer targets for new treatments. Insights into genetics might also lead to the discovery of treatment biomarkers and targets.

SCLC cells are surrounded by an extensive extracellular matrix that includes collagen IV, tenascin, fibronectin, and laminin (figure 6). High expression of these components is associated with a poor prognosis. Adhesion of SCLC cells to the extracellular matrix requires β1-integrins and results in suppression of chemotherapy-induced apoptosis by stimulation of PI3K.[126] The cell cycle arrest and apoptosis normally induced by etoposide is, therefore, prevented.

Several growth factors have been implicated as mediators of autocrine signalling in SCLC, including growth hormone releasing hormone,[127] insulin like growth factor I (IGF-I),[128] bombesin,[129] hepatocyte growth factor,[130] and fibroblast growth factor 2 (FGF2).[131] Inhibitors of several of these growth factor pathways are in clinical development (NCT00896752). For example, FGF2 drives the proliferation of SCLC cells, and confers resistance to etoposide in vitro by upregulation of

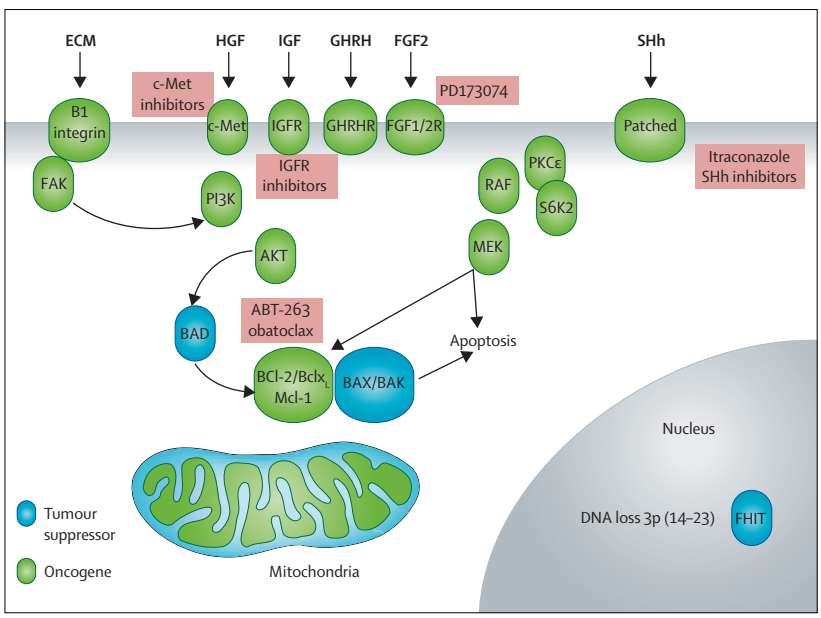


***Figure 6*: Suppression of apoptosis in SCLC cells and interaction with targeted agents**
SCLC cells can suppress apoptosis by increase in stimulation of antiapoptopic pathways via extracellular signals, by desensitisation of the intrinsic cell death machinery via addiction to antiapoptosis proteins, and by mutational burden in genes capable of inducing apoptosis, leading to the loss of proapoptotic tumour suppressors. The pink boxes indicate where investigational targeted agents interact with the the relevant pathways. SCLC=small-cell lung cancer. ECM=extracellular matrix. SHh: sonic hedgehog homologue.

antiapoptotic proteins (Bcl-X_L, Bcl-2, and X-linked IAP) and suppression of the proapoptotic protein BAD. This activity depends on the mitogen-activated protein kinase pathway in a regulatory protein complex comprising RAF, protein kinase C ε type, and S6K.[132] Inhibition of FGF2 signalling by the compound PD173074 impairs SCLC proliferation and chemoresistance, and induces apoptosis in vitro and in vivo. Clinical evaluation of FGF2 inhibitors, therefore, seems warranted.[133] Monoclonal antibodies against IGF-I and hepatocyte growth factor are in clinical development (NCT00940225).

SCLC cells activate the hedgehog signalling pathway, which is involved in embryonic development of the airway epithelium by regulation of morphogenesis and stem-cell fate. In SCLC the hedgehog pathway is abnormal. Activation of the pathway is required to sustain SCLC cells in vitro and in vivo.[134] Mutations of the pathway receptor, however, have not been associated with SCLC. Itraconazole inhibits the hedgehog pathway, by a mechanism distinct from those used by prototype compounds, such as cyclopamine,[135] and might, therefore, become a useful treatment for SCLC tumours that show dependence on hedgehog signalling.

Targeting of the mitochondrial apoptosis pathway is currently being explored as a therapeutic strategy for SCLC. The Bcl-2 family proteins are crucial regulators of apoptosis and have proapoptotic and antiapoptotic roles. The antiapoptotic protein Bcl-2 is overexpressed in SCLC cell lines and primary tissue[136–138] and inhibits the proapoptotic proteins BAX and BAK. These two proteins initiate apoptosis by forming pores in the outer membrane of mitochondria, which leads to the release of other proapoptotic factors, and thereby to activation of caspase enzymes. Activation of BAX requires interaction with other proteins in the Bcl-2 family, such as BID, that harbour the Bcl-2 homology domain BH3, either directly or by the release of bound proapoptotic members (eg, BAD). BAD blocks the antiapoptotic actions of Bcl-2, Bcl-X_L, and Bcl-W.

Study of the interaction between the BAD BH3 domain and Bcl-X_L has led to the discovery of a highly potent small-molecule BAD mimetic called ABT-737 (oral formulation ABT-263). This agent is currently being tested in patients with SCLC (NCT00445198).[139] Although SCLC cell lines have been sensitive to ABT-737 in preclinical studies, resistance to this agent is conferred by expression of the prosurvival Bcl-2 family member Mcl-1.[140] Studies of SCLC cell lines and primary xenograft models established with samples from patients with SCLC suggest that resistance also arises via other mechanisms, such as raised concentrations of proapoptotic BAX, BIM, and NOXA, and reduced concentrations of Mcl-1. A gene expression profile associated with sensitivity indicates involvement of multiple genes linked to apoptosis.[141] Copy number gains at 18q lead to increased expression of Bcl-2 and NOXA, which correlates with sensitivity.[142] These mechanisms of resistance will probably be relevant to studies with ABT-263 and other drug regimens that selectively target Bcl-2, such as antisense oligonucleotides.[143]

Another Bcl-2 inhibitor, obatoclax, is in clinical development as a treatment for SCLC (NCT00682981). By contrast with ABT-737, obatoclax and another compound AT-101 target all antiapoptopic members of the Bcl-2 family, including Mcl-1 (NCT00773955).[144] These agents, but not ABT-737, however, exhibit toxic effects independent of BAX and BAK.

High-throughput sequencing of SCLC samples, coupled with clinical phenotyping, has the potential to reveal information crucial to decyphering chemoresistance. Such knowledge should help to focus development of targeted treatments, especially for relapse. Several small-molecule inhibitors of Src kinase, an enzyme involved in cell migration and adhesion, are in development for relapsing and refractory SCLC (NCT00528645).[145,146]

SCLC is also one of the most hypoxic tumours; more than 60% of patients develop severe hypoxia.[147] This complication is associated with resistance to chemotherapy and radiotherapy and with a raised risk of metastasis. Prevention of hypoxia tolerance has, therefore, become of interest in SCLC.[148] Methods investigated include inhibition of hypoxia-induced factor-1 and autophagy.[149,150]

The advent of next-generation DNA sequencing will enable detailed interrogation of somatic gene alterations and their roles in SCLC. The mutational range of an SCLC cell line, H209, has been established with

massively parallel sequencing technology and revealed 22 910 somatic mutations, of which 134 were in the exome and revealed signatures of tobacco exposure.[151] Specific gene rearrangement in CHD-7, a member of the chromodomain helicase DNA binding domain family of ATP-dependent chromatin remodelling enzymes, has been reported.[151] Comprehensive mapping of other somatic mutations in SCLC might, therefore, lead to identification of crucial gene networks involved in tumorigenesis and reveal potential targets for therapeutic intervention.

The tailoring of therapy with novel agents to individual patient's needs will become the most beneficial approach to treatment of SCLC. In addition to new agents, biomarkers of chemosensitivity will need to be identified to efficaciously assess single agents for relapse after first-line therapy or as maintenance therapy in placebo-controlled, randomised designs.

Conclusions and additional issues

SCLC remains a frustrating disease to research and to treat. In extensive-stage disease new drug combinations and approaches have made little difference to overall survival. Improved survival remains the ultimate goal as, unlike in other chemosensitive cancers, second-line treatment is not an option for most patients.

Although most patients with limited-stage SCLC will also succumb, long-term survival has been improved by good integration of chemotherapy with early, accelerated chest radiotherapy and prophylactic cranial irradiation. A small but notable proportion of patients with SCLC survive long term. After 2 years, the risk of death from the initial disease begins to decrease.[125] The risk of a second primary cancer, however, is 2–10% per patient per year, which is higher than in adult male smokers who have never developed lung cancer. Patients should, therefore, be monitored and refrain from smoking for life.[121] Any new lung mass should undergo biopsy and be tested for early stage NSCLC.[152]

Etoposide and cisplatin remain the mainstays of first-line SCLC treatment. Although the decreasing prevalence of smoking in industrialised countries will be associated with decreasing incidence of SCLC, the burden of disease is shifting to developing countries. Further investment in research for this disease is, therefore, warranted. Many phase 1 and 2 studies of drugs with potential activity in SCLC and phase 2 and 3 trials to improve radiotherapy are underway. Inclusion of patients with SCLC in such trials should be encouraged, especially otherwise healthy patients with relapsing or refractory SCLC, for whom treatment options are limited. A new, effective, and active combination for extensive-stage SCLC would be quickly moved up as a treatment priority.

Contributors

All authors were involved in the literature searches, writing, review, and correction of drafts.

Conflicts of interest

JvM has received money for consultancy from AstraZeneca, Amgen, Pfizer, Hospira, Eli Lilly, Sanofi-Aventis, and GlaxoSmithKline, and for speaking from Eli Lilly, and his institution has received educational grants from Eli Lilly. DAF has received money for consultancy from Merck, Astellas, Genentech, Boehringer Ingelheim, AstraZeneca, Amgen, and Daiichi Sankyo, and for speaking from Merck, Genentech, and Roche. DDR declares that he has no conflicts of interest.

References

1 Härting FH, Hesse W. Der Lungenkrebs, die Bergkrankheit in den Schneeberger Gruben. *Vjschr gerichtl Med offen Sanitats* 1879; **30:** 296–309 (in German).

2 Barnard W. The nature of the 'oat-celled sarcoma' of the mediastinum. *J Pathol* 1926; **29:** 241–44.

3 Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. World Health Organization classification of tumours: pathology and genetics: tumours of the lung, pleura, thymus and heart, vol 10. Lyon: IARC Press, 2004. http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb10/bb10-cover.pdf (accessed Feb 16, 2011).

4 National Cancer Institute. SEER Cancer Statistics Review, 1975–2006. http://seer.cancer.gov/csr/1975_2006 (accessed Feb 7, 2011).

5 Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rising. *Int J Cancer* 2005; **117:** 294–99.

6 Antony GK, Bertino E, Franklin M et al. Small cell lung cancer in never smokers. Report of 2 cases. *J Thorac Oncol* 2010; **5:** 747–48.

7 Rudin CM, Avila-Tang E, Harris CC, et al. Lung cancer in never smokers: molecular profiles and therapeutic implications. *Clin Cancer Res* 2009; **15:** 5646–61.

8 Field JK, Duffy SW. Lung cancer screening: the way forward. *Br J Cancer* 2008; **99:** 557–62.

9 Franklin WF, Noguchi M, Gonzalez A. Molecular and cellular pathology of lung cancer. In: Pass HI, Carbone DP, Johnson DH, Minna JD, Scagliotti GV, Turrisi AT, eds. Principles and practice of lung cancer, 4th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2010: 287–324.

10 Meyerson M, Franklin WA, Kelley MJ. Molecular classification and molecular genetics of human lung cancers. *Semin Oncol* 2004; **31:** 4–19.

11 Coe BP, Lee EH, Chi B et al. Gain of a region on 7p22.3, containing *MAD1L1*, is the most frequent event in small-cell lung cancer cell lines. *Genes Chromosomes Cancer* 2006; **45:** 11–19.

12 Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000; **100:** 57–70.

13 Watson WL, Berg JW. Oat cell lung cancer. *Cancer* 1962; **15:** 759–68.

14 De Ruysscher D, Botterweck A, Dirx M, et al. Eligibility for concurrent chemotherapy and radiotherapy of locally advanced lung cancer patients: a prospective, population-based study. *Ann Oncol* 2009; **20:** 98–102.

15 Masters GA. Clinical presentation of small cell lung cancer. In: Pass HI, Carbone DP, Johnson DH, Minna JD, Scagliotti GV, Turrisi AT, eds. Principles and practice of lung cancer, 4th edn. Philadelphia, PA: Lippincott Williams & Wilkins. Philadelphia. 2010: 341–51.

16 Wilson LD, Detterbeck F, Yahalom D. Superior Vena cava syndrome with malignant causes. *N Engl J Med* 2007; **356:** 1862–69.

17 Ellison DH, Berl T. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; **356:** 2064–72.

18 Chute JP, Taylor E, Williams J, Kaye F, Venzon D, Johnson BE. A metabolic study of patients with lung cancer and hyponatremia of malignancy. *Clin Cancer Res* 2006; **12:** 888–96.

19 Terzolo M, Reimondo G, Ali A, et al. Ectopic ACTH syndrome: molecular bases and clinical heterogeneity. *Ann Oncol* 2001; **12** (suppl 2)**:** S83–87.

20 Boscaro M, Arnaldi G. Approach to the patient with possible Cushing's syndrome. *J Clin Endocrinol Metab* 2009; **94:** 3121–31.

21 Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. *N Engl J Med* 2003; **349:** 1543–54.

22 Payne M, Bradbury P, Lang B, et al. Prospective study into the incidence of Lambert Eaton myasthenic syndrome in small cell lung cancer. *J Thorac Oncol* 2010; **5:** 34–38.

23 Maddison P, Newsom-Davis J, Mills KR, Souhami RL. Favourable prognosis in Lambert-Eaton myasthenic syndrome and small-cell lung carcinoma. *Lancet* 1999; **353:** 117–18.

24 Wirtz PW, Lang B, Graus F, et al. P/Q-type calcium channel antibodies, Lambert-Eaton myasthenic syndrome and survival in small cell lung cancer. *J Neuroimmunol* 2005; **164:** 161–65.

25 Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain* 2000; **123:** 1481–94.

26 Maddison P, Lang B. Paraneoplastic neurological autoimmunity and survival in small-cell lung cancer. *J Neuroimmunol* 2008; **201:** 159–62.

27 Monstad SE, Drivsholm L, Storstein A, et al. Hu and voltage-gated calcium channel (VGCC) antibodies related to the prognosis of small-cell lung cancer. *J Clin Oncol* 2004; **22:** 795–800.

28 Gandhi L, Johnson BE. Paraneoplastic syndromes associated with small cell lung cancer. *J Natl Compr Canc Netw* 2006; **4:** 631–38.

29 Titulaer MJ, Klooster R, Potman M, et al. SOX Antibodies in small-cell lung cancer and Lambert-Eaton myasthenic syndrome: frequency and relation with survival. *J Clin Oncol* 2009; **27:** 4260–67.

30 Graus F, Dalmou J, Rene R, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. *J Clin Oncol* 1997; **15:** 2866–72.

31 Zelen M. Keynote address on biostatistics and data retrieval. *Cancer Chemother Rep* 1973; **4:** 31–42.

32 Goldstraw P, ed. IASLC staging handbook in thoracic oncology, 1st edn. Orange Park, FL: Editorial Rx Press, 2009.

33 Shepherd FA, Crowley J, Van Houtte P, et al, for the International Association for the Study of Lung Cancer International Staging. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumour, node, metastasis classification for lung cancer. *J Thorac Oncol* 2007; **2:** 1067–77.

34 Kato Y, Ferguson TB, Bennett DE, et al. Oat cell carcinoma of the lung. A review of 138 cases. *Cancer* 1969; **23:** 517–24.

35 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:** 146–49.

36 Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. *J Clin Oncol* 1990; **8:** 1563–74.

37 Sagman U, Maki E, Evans WK, et al. Small-cell carcinoma of the lung: derivation of a prognostic staging system. *J Clin Oncol* 1991; **9:** 1639–49.

38 Paesmans MN, Sculier JP, Lecomte J, et al. Prognostic factors for patients with small cell lung carcinoma: analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. *Cancer* 2000; **89:** 523–33.

39 Sculier JP, Chansky K, Crowley JJ, Van Meerbeeck JP, Goldstraw P, on behalf of the International Staging Committee and Participating Institutions. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th edition of the TNM classification of malignant tumours and the proposals for the 7th edition. *J Thorac Oncol* 2008; **3:** 457–66.

40 Foster NR, Mandrekar SJ, Schild SE, et al. Prognostic factors differ by tumour stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. *Cancer* 2009; **115:** 2721–31.

41 Nicholson SA, Beasley MB, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathological study of 100 cases with surgical specimens. *Am J Surg Pathol* 2002; **26:** 1184–97.

42 Paesmans MN, Lafitte JJ, Lecomte JN, et al. Validation and comparison of published prognostic classifications for small cell lung cancer. *J Thorac Oncol* 2010; **5** (suppl 1): s104 (abstr 265O).

43 Sørensen M, Pijls-Johannesma M, Felip E, for the ESMO Guidelines Working Group. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): v120–25.

44 Simon GR, Turrisi A. Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; **132** (suppl 3)**:** 324S–39S.

45 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. small cell lung cancer. www.nccn.org/professionals/physician_gls/PDF/sclc.pdf (accessed Feb 7, 2011).

46 Seute T, Leffers P, ten Velde GPM, et al. Detection of brain metastases from small cell lung cancer—consequences of changing imaging techniques (CT versus MRI). *Cancer* 2008; **112:** 1827–34.

47 Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J* 2009; **34:** 17–41.

48 van Loon J, De Ruysscher D, Wanders R, et al. Selective nodal irradiation on basis of 18FDG-PET scans in limited-disease small-cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys* 2010; **77:** 329–36.

49 Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985; **312:** 1604–08.

50 Karnofsky DA, Abelman WH, Craver LF, et al. Use of nitrogen mustards in the palliative treatment of cancer, with particular reference to bronchiogenic carcinoma. *Cancer* 1948; **1:** 634–56.

51 Scadding JG, Bignall JR, Blair LG, et al. Comparative trial of surgery and radiotherapy for the primary treatment of small-celled, or oat-celled carcinoma of the bronchus: first report to the Medical Research Council by the working-party on the evaluation of different methods of therapy in carcinoma of the bronchus. *Lancet* 1966; **2:** 979–86.

52 Green RA, Humphrey E, Close H, Patno ME. Alkylating agents in bronchogenic carcinoma. *Am J Med* 1969; **46:** 516–25.

53 Lowenbraun S, Bartolucci A, Smalley RV, Lynn M, Krauss S, Durant JR. The superiority of combination chemotherapy over single agent chemotherapy in small cell lung carcinoma. *Cancer* 1979; **44:** 406–13.

54 Pelayo Alvarez M, Gallego Rubio Ó, Bonfill Cosp X, Agra Varela Y. Chemotherapy versus best supportive care for extensive small cell lung cancer. *Cochrane Database Syst Rev* 2009; **4:** CD001990.

55 Lally BE, Urbanic JJ, Blackstock AW, Miller AA, Perry MC. Small cell lung cancer: have we made any progress over the last 25 years? *Oncologist* 2007; **12:** 1096–104.

56 Oze I, Hotta K, Kiura K, et al. Twenty-seven years of phase III trials for patients with extensive disease small-cell lung cancer: disappointing results. *PLoS One* 2009; **4:** e7835.

57 Seifter EJ, Ihde DC. Therapy of small cell lung cancer: a perspective on two decades of clinical research. *Semin Oncol* 1988; **15:** 278–99.

58 Hirsch FR, Hansen HH, Hansen M, et al. The superiority of combination chemotherapy including etoposide based on in vivo cell cycle analysis in the treatment of extensive small-cell lung cancer: a randomized trial of 288 consecutive patients. *J Clin Oncol* 1987; **5:** 585–91.

59 Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol* 1985; **3:** 1471–77.

60 Sundstrøm S, Bremnes RM, Kaasa S, 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.

61 Giordano KF, Jatoi A, Adjei AA, et al. Ramifications of severe organ dysfunction in newly diagnosed patients with small cell lung cancer: contemporary experience from a single institution. *Lung Cancer* 2005; **49:** 209–15.

62 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.

63 Mascaux C, Paesmans M, Berghmans T, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. *Lung Cancer* 2000; **30:** 23–36.

64 Amarasena IU, Walters JA, Wood-Baker R, et al. Platinum versus non-platinum chemotherapy regimens for small cell lung cancer. *Cochrane Database Syst Rev* 2008; **4:** CD006849.

65 Okamoto H, Watanabe K, Kunikane H, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *Br J Cancer* 2007; **97:** 162–69.

66 Jiang J, Liang X, Zhou X, et al. A meta-analysis of randomized controlled trials comparing irinotecan/platinum with etoposide/platinum in patients with previously untreated extensive-stage small cell lung cancer. *J Thorac Oncol* 2010; **5:** 867–73.

67 Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2001; **346:** 85–91.

68 Hermes A, Bergman B, Bremnes R, et al. Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial. *J Clin Oncol* 2008; **26:** 4261–67.

69 Hanna N, Bunn PA, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006; **24:** 2038–43.

70 Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *J Clin Oncol* 2009; **27:** 2530–35.

71 Ando Y, Ueoka H, Sugiyama T, Ichiki M, Shimokata K, Hasegawa Y. Polymorphisms of UDP-glucuronosyltransferase and pharmacokinetics of irinotecan. *Ther Drug Monit* 2002; **24:** 111–16.

72 Inoue A, Ishimoto O, Fukumoto S, et al. A phase II study of amrubicin combined with carboplatin for elderly patents with small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0405. *Ann Oncol* 2010; **21:** 800–03.

73 Demedts I, Vermaelen K, van Meerbeeck JP. Treatment of ES-SCLC: current status and future prospects. *Eur Respir J* 2010; **35:** 202–15.

74 Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. *J Clin Oncol* 1999; **17:** 2092–99.

75 Postmus PE, Haaxma-Reiche H, Smit EF, et al. Treatment of brain metastases of small-cell lung cancer: comparing teniposide and teniposide with whole-brain radiotherapy—a phase III study of the European Organization for the Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol* 2000; **18:** 3400–08.

76 Furuse K, Kamimori T, Kawahara M et al. A pilot study of concurrent whole-brain radiotherapy and chemotherapy combined with cisplatin, vindesine and mitomycin in non-small-cell lung cancer with brain metastasis. *Br J Cancer* 1997; **75:** 614–18.

77 Robinet G, Thomas P, Breton JL, et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Français de Pneumo-Cancérologie (GFPC) Protocol 95-1. *Ann Oncol* 2001; **12:** 59–67.

78 Neuhaus T, Ko Y, Muller RP, et al. A phase III trial of topotecan and whole brain radiation therapy for patients with CNS-metastases due to lung cancer. *Br J Cancer* 2009; **100:** 291–97.

79 Lad T, Piantadosi S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest* 1994; **106** (6 suppl): 320S–23S.

80 Lim E, Belcher E, Yap YK, et al. The role of surgery in the treatment of limited disease small cell lung cancer: time to reevaluate. *J Thorac Oncol* 2008; **3:** 1267–71.

81 Yu JB, Decker RH, Detterbeck F, Wilson LD. Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. *J Thorac Oncol* 2010; **5:** 215–19.

82 Shepherd FS. Surgery for limited stage small cell lung cancer. Time to fish or cut bait. *J Thorac Oncol* 2010 **5:** 147–49.

83 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.

84 Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol* 1992; **10:** 890–95.

85 Kosmidis PA, Samantas E, Fountzilas G, et al. Cisplatin/etoposide versus carboplatin/etoposide chemotherapy and irradiation in small cell lung cancer: a randomized phase III study. Hellenic Cooperative Oncology Group for Lung Cancer Trials. *Semin Oncol* 1994; **21:** 23–30.

86 Ettinger DS, Berkey BA, Abrams RA, et al. Study of paclitaxel, etoposide, and cisplatin chemotherapy combined with twice-daily thoracic radiotherapy for patients with limited-stage small-cell lung cancer: a Radiation Therapy Oncology Group 9609 phase II study. *J Clin Oncol* 2005; **23:** 4991–98.

87 Han JY, Cho KH, Lee DH, et al. Phase II study of irinotecan plus cisplatin induction followed by concurrent twice-daily thoracic irradiation with etoposide plus cisplatin chemotherapy for limited-disease small-cell lung cancer. *J Clin Oncol* 2005; **23:** 3488–94.

88 Hanna N, Ansari R, Fisher W, et al. Etoposide, ifosfamide and cisplatin (VIP) plus concurrent radiation therapy for previously untreated limited small cell lung cancer (SCLC): a Hoosier Oncology Group (HOG) phase II study. *Lung Cancer* 2002; **35:** 293–97.

89 Saito H, Takada Y, Ichinose Y, et al. Phase II study of etoposide and cisplatin with concurrent twice-daily thoracic radiotherapy followed by irinotecan and cisplatin in patients with limited-disease small-cell lung cancer: West Japan Thoracic Oncology Group 9902. *J Clin Oncol* 2006; **24:** 5247–52.

90 Edelman MJ, Chansky K, Gaspar LE, et al. Phase II trial of cisplatin/etoposide and concurrent radiotherapy followed by paclitaxel/carboplatin consolidation for limited small-cell lung cancer: Southwest Oncology Group 9713. *J Clin Oncol* 2004; **22:** 127–32.

91 De Ruysscher D, Vansteenkiste J. Chest radiotherapy in limited-stage small cell lung cancer: facts, questions, prospects. *Radiother Oncol* 2000; **55:** 1–9.

92 De Ruysscher D, Bremer RH, Koppe F,et al. Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: a phase II trial. *Radiother Oncol* 2006; **80:** 307–12.

93 Pijls-Johannesma M, De Ruysscher D, Vansteenkiste J, et al. Timing of chest radiotherapy in patients with limited stage small cell lung cancer: a systematic review and meta-analysis of randomised controlled trials. *Cancer Treat Rev* 2007; **33:** 461–73.

94 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:** 4837–45.

95 Turrisi AT, Kim K, Blum R, 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.

96 De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol* 2006; **24:** 1057–63.

97 Postmus PE, Haaxma-Reiche H, Gregor A, et al. Brain-only metastases of small cell lung cancer; efficacy of whole brain radiotherapy. An EORTC phase II study. *Radiother Oncol* 1998; **46:** 29–32.

98 The Prophylactic Cranial Irradiation Overview Collaborative Group. Cranial Irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission *Cochrane Database Syst Rev* 2000; **4:** CD002805.

99 Le Péchoux C, Dunant A, Senan S, et al, for the Prophylactic cranial irradiation (PCI) Collaborative Group. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol* 2009; **10:** 467–74.

100 Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2010; published online Aug 26. DOI:10.1016/j.ijrobp.2010.05.013.

101 Slotman B, Faivre-Finn C, Kramer G, et al, for the EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007; **357:** 664–72.

102 Arriagada R, Le Chevalier T, Borie F et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. *J Natl Cancer Inst* 1995; **87:** 183–90.

103 Gregor A, Cull A, Stephens RJ et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer* 1997; **33:** 1752–58.

104 Grosshans DR, Meyers CA, Allen PK, et al. Neurocognitive function in patients with small cell lung cancer—Effect of prophylactic cranial irradiation. *Cancer* 2008; **112:** 589–95.

105 Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D, Delattre JY. CNS complications of radiotherapy and chemotherapy. *Lancet* 2009; **37:** 1639–51.

106 Sundstrøm S, Bremnes RM, Kaasa S, Aasebo U, Aamdal S. Second-line chemotherapy in recurrent small cell lung cancer. Results from a crossover schedule after primary treatment with cisplatin and etoposide (EP-regimen) or cyclophosphamide, epirubicin, and vincristin (CEV-regimen). *Lung Cancer* 2005; **48:** 251–61.

107 O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol* 2006; **24:** 5441–47.

108 Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007; **25:** 2086–92.

109 von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999; **17:** 658–67.

110 Puglisi M, Dolly S, Faria A, et al. Treatment options for small cell lung cancer—do we have more choice? *Br J Cancer* 2010; **102:** 629–38.

111 Inoue A, Sugawara S, Yamazaki K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group trial 0402. *J Clin Oncol* 2008; **26:** 5401–06.

112 Eckardt JR, Bentsion DL, Lipatov ON, et al. Phase II study of picoplatin as second-line therapy for patients with small-cell lung cancer. *J Clin Oncol* 2009; **27:** 2046–51.

113 Ciuleanu T, Samarzjia M, Demidchik Y, et al. Randomized phase III study (SPEAR) of picoplatin plus best supportive care (BSC) or BSC alone in patients (pts) with SCLC refractory or progressive within 6 months after first-line platinum-based chemotherapy. *J Clin Oncol* 2010; **28:** (15 suppl): 7002 (abstr).

114 Rossi A, Maione P, Palazzolo G, et al. New targeted therapies and small cell lung cancer. *Clin Lung Cancer* 2008; **9:** 271–79.

115 Akl EA, Kamath G, Kim SY, et al. Oral anticoagulation for prolonging survival in patients with cancer. *Cochrane Database Syst Rev* 2007; **2:** CD006466.

116 Akl EA, van Doormaal FF, Barba M, et al. Parenteral anticoagulation may prolong the survival of patients with limited small cell lung cancer: a Cochrane systematic review. *J Exp Clin Cancer Res* 2008; **27:** 4.

117 Khanzada UK, Pardo OE, Meier C, et al. Potent inhibition of small-cell lung cancer cell growth by simvastatin reveals selective functions of Ras isoforms in growth factor signalling. *Oncogene* 2006; **25:** 877–87.

118 Weiss RH, Ramirez AL, Joo A. Short-term pravastatin mediates growth inhibition and apoptosis, independently of Ras, via the signaling proteins p27Kip1 and PI3 kinase. *J Am Soc Nephrol* 1999; **10:** 1880–90.

119 Mazza R, Lina M, Boffi R, et al. Taking care of smoker cancer patients: a review and some recommendations. *Ann Oncol* 2010; **21:** 1404–09.

120 Gritz ER, Vidrine DJ, Lazev AB. Smoking cessation in cancer patients. Never too late to quit. In: DeVoss DN, Given CW, Given B, Champion VL, eds. Evidence-based cancer care and prevention: behavioral interventions. New York, NY: Springer Publishing, 2003: 107–40.

121 Garces YI, Schroeder DR, Nirelli LM, et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. *Chest* 2004; **126:** 1733–41.

122 Monson JM, Stark P, Reilly JJ, et al. Clinical radiation pneumonitis and radiographic changes after thoracic radiation therapy for lung carcinoma. *Cancer* 1998; **82:** 842–50.

123 Dehing-Oberije C, De Ruysscher D, van Baardwijk A, et al. The importance of patient characteristics for the prediction of radiation-induced lung toxicity. *Radiother Oncol* 2009; **91:** 421–26.

124 Sagman U. Second primary malignancies following diagnosis of small cell lung cancer. *J Clin Oncol* 1992; **10:** 1525–33.

125 Tucker MA, Murray N, Shaw EG, et al. Second primary cancers related to smoking and treatment of small-cell lung cancer. *J Natl Cancer Inst* 1997; **89:** 1782–88.

126 Hodkinson PS, Elliott T, Wong WS, et al. ECM overrides DNA damage-induced cell cycle arrest and apoptosis in small-cell lung cancer cells through beta1 integrin-dependent activation of PI3-kinase. *Cell Death Differ* 2006; **13:** 1776–88.

127 Kiaris H, Schally AV, Varga JL, Groot K, Armatis P. Growth hormone-releasing hormone: an autocrine growth factor for small cell lung carcinoma. *Proc Natl Acad Sci USA* 1999; **96:** 14894–98.

128 Warshamana-Greene GS, Litz J, Buchdunger E, et al. The insulin-like growth factor-I receptor kinase inhibitor, NVP-ADW742, sensitizes small cell lung cancer cell lines to the effects of chemotherapy. *Clin Cancer Res* 2005; **11:** 1563–71.

129 Cuttitta F, Carney DN, Mulshine J, et al. Bombesin-like peptides can function as autocrine growth factors in human small-cell lung cancer. *Nature* 1985; **316:** 823–26.

130 Ma PC, Tretiakova MS, Nallasura V, et al. Downstream signalling and specific inhibition of c-MET/HGF pathway in small cell lung cancer: implications for tumour invasion. *Br J Cancer* 2007; **97:** 368–77.

131 Pardo OE, Arcaro A, Salerno G, et al. Fibroblast growth factor-2 induces translational regulation of Bcl-X_L and Bcl-2 via a MEK-dependent pathway: correlation with resistance to etoposide-induced apoptosis. *J Biol Chem* 2002; **277:** 12040–46.

132 Pardo OE, Wellbrock C, Khanzada UK, et al. FGF-2 protects small cell lung cancer cells from apoptosis through a complex involving PKCε, B-Raf and S6K2. *EMBO J* 2006; **25:** 3078–88.

133 Pardo OE, Latigo J, Jeffery RE, et al. The fibroblast growth factor receptor inhibitor PD173074 blocks small cell lung cancer growth in vitro and in vivo. *Cancer Res* 2009; **69:** 8645–51.

134 Watkins DN, Berman DM, Burkholder SG, et al. Hedgehog signalling within airway epithelial progenitors and in small-cell lung cancer. *Nature* 2003; **422:** 313–17.

135 Kim J, Tang JY, Gong R, et al. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. *Cancer Cell* 2010; **17:** 388–99.

136 Ikegaki N, Katsumata M, Minna J, Tsujimoto Y. Expression of bcl-2 in small cell lung carcinoma cells. *Cancer Res* 1994; **54:** 6–8.

137 Jiang SX, Sato Y, Kuwao S, Kameya T. Expression of bcl-2 oncogene protein is prevalent in small cell lung carcinomas. *J Pathol* 1995; **177:** 135–38.

138 Kaiser U, Schilli M, Haag U, et al. Expression of bcl-2-protein in small cell lung cancer. *Lung Cancer* 1996; **15:** 31–40.

139 Oltersdorf T, Elmore SW, Shoemaker AR, et al. An inhibitor of Bcl-2 family proteins induces regression of solid tumours. *Nature* 2005; **435:** 677–81.

140 Tahir SK, Yang X, Anderson MG, et al. Influence of Bcl-2 family members on the cellular response of small-cell lung cancer cell lines to ABT-737. *Cancer Res* 2007; **67:** 1176–83.

141 Tahir SK, Wass J, Joseph MK, et al. Identification of expression signatures predictive of sensitivity to the Bcl-2 family member inhibitor ABT-263 in small cell lung carcinoma and leukemia/lymphoma cell lines. *Mol Cancer Ther* 2010; **9:** 545–57.

142 Olejniczak ET, Van Sant C, Anderson MG, et al. Integrative genomic analysis of small-cell lung carcinoma reveals correlates of sensitivity to bcl-2 antagonists and uncovers novel chromosomal gains. *Mol Cancer Res* 2007; **5:** 331–39.

143 Rudin CM, Salgia R, Wang X, et al. Randomized phase II Study of carboplatin and etoposide with or without the bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103. *J Clin Oncol* 2008; **26:** 870–76.

144 Paik PK, Rudin CM, Brown A, et al. A phase I study of obatoclax mesylate, a Bcl-2 antagonist, plus topotecan in solid tumor malignancies. *Cancer Chemother Pharmacol* 2010: **66:** 1079–85.

145 Rothschild SI, Gautschi O, Haura EB, Johnson FM. Src inhibitors in lung cancer: current status and future directions. *Clin Lung Cancer* 2010; **11:** 238–42.

146 Miller AA, Pang H, Hodgson L, et al, for the Cancer and Leukemia Group B (CALGB). A phase II study of dasatinib in patients with chemosensitive relapsed small cell lung cancer (Cancer and Leukemia Group B 30602). *J Thorac Oncol* 2010; **5:** 380–84.

147 Ioannou M, Papamichali R, Kouvaras E, et al. Hypoxia inducible factor-1 alpha and vascular endothelial growth factor in biopsies of small cell lung carcinoma. *Lung* 2009; **187:** 321–29.

148 Lee ST, Scott AM. Hypoxia positron emission tomography imaging with 18F-fluoromisonidazole. *Semin Nucl Med* 2007; **37:** 451–61.

149 Jacoby JJ, Erez B, Korshunova MV, et al. Treatment with HIF-1α antagonist PX-478 inhibits progression and spread of orthotopic human small cell lung cancer and lung adenocarcinoma in mice. *J Thorac Oncol* 2010; **5:** 940–49.

150 Rouschop KM, van den Beucken T, Dubois L, et al. The unfolded protein response protects human tumour cells during hypoxia through regulation of the autophagy genes *MAP1LC3B* and *ATG5*. *J Clin Invest* 2010; **120:** 127–41.

151 Pleasance ED, Stephens PJ, O'Meara S, et al. A small-cell lung cancer genome with complex signatures of tobacco exposure. *Nature* 2010; **463:** 184–90.

152 Smythe WR. Surgical resection of non-small cell lung cancer after treatment of small cell carcinoma. *Ann Thorac Surg* 2001; **71:** 962–66.

Non-small-cell lung cancer

Peter Goldstraw, David Ball, James R Jett, Thierry Le Chevalier, Eric Lim, Andrew G Nicholson, Frances A Shepherd

In the decade since the last *Lancet* Seminar on lung cancer there have been advances in many aspects of the classification, diagnosis, and treatment of non-small-cell lung cancer (NSCLC). An international panel of experts has been brought together to focus on changes in the epidemiology and pathological classification of NSCLC, the role of CT screening and other techniques that could allow earlier diagnosis and more effective treatment of the disease, and the recently introduced seventh edition of the TNM classification and its relation to other prognostic factors such as biological markers. We also describe advances in treatment that have seen the introduction of a new generation of chemotherapy agents, a proven advantage to adjuvant chemotherapy after complete resection for specific stage groups, new techniques for the planning and administration of radiotherapy, and new surgical approaches to assess and reduce the risks of surgical treatment.

Lancet 2011; 378: 1727–40
Published Online
May 11, 2011
DOI:10.1016/S0140-6736(10)62101-0

See Editorial page 1678

Academic Department of Thoracic Surgery (Prof P Goldstraw FRCS, E Lim FRCS) **and Department of Histopathology** (Prof A G Nicholson FRCPath), **Royal Brompton and Harefield NHS Foundation Trust and Imperial College School of Medicine, London, UK; Division of Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, and the University of Melbourne, Melbourne, VIC, Australia** (Prof D Ball FRANZCR)**; Mayo Clinic College of Medicine, Rochester, MN, USA** (J R Jett MD)**; Institut Gustave-Roussy, Villejuif, France** (T Le Chevalier MD)**; and Princess Margaret Hospital, Toronto, ON, Canada** (F A Shepherd MD)

Correspondence to:
Prof Peter Goldstraw, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK
p.goldstraw@rbht.nhs.uk

Advances in pathology

The last *Lancet* Seminar on non-small-cell lung cancer (NSCLC) was published in 2000, with no mention of the advancing molecular age,[1] and although the 2004 WHO classification of lung tumours introduced relevant genetic data,[2] rapid development in this area has necessitated an almost immediate update, specifically relating to adenocarcinoma and diagnosis on the basis of biopsies and cytological material.[3] A key aspect of this recent update was the multidisciplinary and international composition of its review panel,[4] since previous classifications were criticised for having been written "for pathologists by pathologists" and because they were based on reporting resections, which include only a minority of cases. Therefore, although NSCLC continues to serve as an umbrella clinical term for adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, and more poorly differentiated variants, a key recent advance is the increasing refinement of a pathological diagnosis of NSCLC-NOS (not otherwise specified) whenever possible. This change was mainly therapy-driven—for example, pemetrexed has no or little activity in squamous-cell carcinoma, and bevacizumab, an antiangiogenic agent, has excessive toxic effects in squamous-cell carcinoma. Furthermore, in biopsy and cytology material, immunohistochemistry is being used to distinguish adenocarcinoma from squamous-cell carcinoma if morphological criteria used in resections are not apparent, with subsequent refinement of classification on the basis of the immunoprofile.[3] Thyroid transcription factor 1, cytokeratin 7, and mucin staining are recommended markers for adenocarcinoma, and P63 and cytokeratin 5/6 for squamous-cell carcinoma[5,6]—data that were validated in biopsies and are applicable to cytological samples.[7,8] The importance of multidisciplinary review is emphasised in discussion of whether molecular data should be sought, the need for further sampling, and whether clinical features might assist in planning of future management. The pathologist should now be part of these discussions, not least to ensure judicious use of tissue—in particular, preservation of positive cytological specimens.

A more controversial recommendation is to discontinue use of the term bronchioloalveolar carcinoma, mainly because of the absence of standardised criteria across disciplines.[4] For example, pathologists have reserved the term bronchioloalveolar carcinoma for adenocarcinoma-in-situ since 1999,[2] whereas oncologists continue to use this term to include advanced disease,[9] meaning that published data have been difficult to compare. Tumours with no invasive component (mainly seen in east Asian cohorts or in those relating to screening trials) should now be termed adenocarcinoma-in-situ, with an additional minimally invasive category, since data suggest that an invasive area of 5 mm or less has an improved prognosis.[10] For resected invasive tumours (those typically seen in most diagnostic practices), non-mucinous tumours should be assessed in relation to five major patterns—micropapillary[11] being added to lepidic (formally bronchioloalveolar, and literally meaning scale-like), papillary, acinar, and solid. Of these, the predominant histological pattern should be documented since this characteristic seems to be related to prognosis, predicting recurrence in stage I tumours,[12] common gene mutations, and gene-profiling data.[13] The mixed pattern proposed in 2004 proved redundant since nearly 95% of cases fell into this category.

Mucinous adenocarcinomas are now viewed as a variant, often presenting with multicentric consolidation, perhaps reflecting aerogenous spread. They are typically *KRAS*-mutation positive and *EGFR*-mutation negative.[14] Previously, these variants would have been classified as mucinous bronchioloalveolar carcinoma, but they typically contain invasive foci, again reflecting the problem with the term bronchioloalveolar carcinoma. As

Search strategy and selection criteria

The literature search for each section was based on a search of Medline and PubMed for the years since the previous *Lancet* Seminars on this topic (2000 and 2005) and 2009 inclusive. We searched for English language articles only, using the keywords "carcinoma, non-small cell" and the specific terms used in the title of each section. Additional references were taken from review articles and the individual authors' own publications.

with non-mucinous tumours, reporting of the predominant pattern is recommended.

Notably, variants still include the rare fetal adenocarcinoma since this disease has a good prognosis,[2] but clear-cell and signet ring morphologies have been removed. However, even before the ink was dry on these revisions, data emerged linking signet ring morphology to the EML4–ALK gene fusion mutation[15]—a molecular abnormality with potential for targeted treatment.

On a broader level, the seventh TNM staging revision[16] has brought additional responsibility to the pathologist, not only in providing a minimum dataset, but proposing that microscopic examination by the pathologist be used to distinguish synchronous primaries from satellite nodules, rather than clinical documentation of their macroscopic presence as multifocal tumours. The revision also called for further investigation into the relevance of histopathological criteria to TNM staging—for example, extent of pleural invasion[17]—and pathologists should involve themselves in groups informing the eight revision.

For the **National Lung Screening Trial website** see http://cancer.gov/nlst/updates

The next few years will undoubtedly see an increased need for immunohistochemical and genetic data to inform treatment response and prognosis in well resourced countries, probably for all NSCLCs and not only adenocarcinoma. However, although a giant stride has been made in making classification more relevant to preclinical data and patient management, the importance of routine morphological diagnosis should not be forgotten. The classification of NSCLC has to remain globally applicable, with only routine staining and basic therapy available in many resource-poor countries. Even in the high-technology setting, morphological review has proved as accurate as gene profiling in distinguishing of synchronous primaries from satellite nodules. It is undoubtedly cheaper.[18] We are seeing the dawn of targeted treatment for NSCLC, with several predictive if not prognostic markers on the borders of clinical use.[19] As examples, testing for ERCC1, thymidylate synthase, and RRM1 in relation to activities of platin-based, pemetrexed-based, and gemcitabine-based therapies, respectively, might not be far away. Not only should the pathologist adapt to manage tissue wisely and classify appropriately to inform this process, they should work to validate these potential advances. Furthermore, other disciplines should adhere to the new categorisation,[4] so that consensus terminology is used not only for diagnosis, but in research cohorts globally, especially in drug trials.

Advances in early diagnosis

Routine screening for lung cancer is not currently recommended by any major medical organisation. Several phase 2 non-randomised trials of CT screening of high-risk individuals (current or former smokers with 20 pack-years of smoking) have yielded enticing results.[20–22] They have shown that CT screening detects small-sized lung cancers of 12–15 mm in diameter. Chest radiographs have been shown to miss 70–80% of the cancers that are detected by CT. In prevalence studies, 60–80% of detected cancers are stage I. When CT screening results were compared with those of a validated control group, CT detected three times more lung cancer than would be expected, and resulted in ten times more thoracic operations than were expected.[23] Additionally, no decreases in advanced stage cancers or lung-cancer deaths occurred.[23,24] To date, several small randomised controlled screening trials have been reported, but they have been too small to assess whether CT screening reduces mortality.[24–26] The two large randomised trials that could definitively address the ability of CT screening to decrease lung-cancer mortality are the National Lung Cancer Screening Trial (NLST) and the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial. Mortality results from those two trials are expected in 2011 and 2015, respectively. A report from the NELSON trial[27] validated the use of CT volumetric assessment of nodules to assess malignant disease and to determine which nodules should be treated surgically.

As this report was going to press, the US National Cancer Institute announced that the NLST was being closed because the primary endpoint of the study had been met. The CT screening group demonstrated a 20% mortality reduction in lung cancer as compared with chest x-ray screening. Additionally, a 6·9% overall mortality reduction was observed in the CT group. Limited data are available from the NLST website. Peer-reviewed reports with more details are expected in late spring, 2011.

Much effort is underway to identify susceptibility genes for lung cancer, with particular interest in 15q24–25, which is strongly associated with the disease.[28,29] This region contains several genes of interest, including three genes that encode nicotinic acetylcholine receptor subunits. However, these genes could simply be associated with nicotine dependence.[28] An enormous research effort is underway related to biomarkers in airway epithelial cells, blood, sputum, breath, and urine for early diagnosis or prediction of high risk. Airway epithelial gene expression and predisposition to lung cancer is under investigation by at least two different groups using an 80-gene and a 14-gene expression biomarker assay, respectively.[30,31] Blood biomarkers have included novel proteins and autoantibodies to tumour-associated antigens that might be detectable 1–3 years before clinical diagnosis.[32–34] Qiu and colleagues[34] evaluated a panel of three autoantibodies to annexin I, 14-3-3 theta, and RPSA (also known as LAMR1) in a case-controlled study. They reported a sensitivity of 51%, specificity of 82%, and area under the receiver-operator characteristic curve of 0·73 for prediction or detection of lung cancer up to a year before clinical diagnosis.[34]

Fluorescence in-situ hybridisation (FISH) detection of genomic changes of cytology or bronchial tissue has been associated with increased risk of lung cancer.[35,36] Varella-Garcia and colleagues[35] evaluated four

Panel 1: **The T, N, and M descriptors in the seventh edition of the TNM classification for lung cancer[42]**

T—primary tumour

TX: Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings, but not visualised by imaging or bronchoscopy
T0: No evidence of primary tumour
Tis: Carcinoma in situ
T1: Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)
T1a: Tumour 2 cm or less in greatest dimension*
T1b: Tumour more than 2 cm but not more than 3 cm in greatest dimension
T2: Tumour more than 3 cm but not more than 7 cm; or tumour with any of the following features†:
- Involves main bronchus, 2 cm or more distal to the carina
- Invades visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a: Tumour more than 3 cm but not more than 5 cm in greatest dimension
T2b: Tumour more than 5 cm but not more than 7 cm in greatest dimension
T3: Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumour in the main bronchus less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe as the primary.
T4: Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary.

N—regional lymph nodes

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

M—distant metastasis

M0: No distant metastasis
M1: Distant metastasis
M1a: Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural or pericardial effusion‡
M1b: Distant metastasis

The resultant stage groupings are:

Occult carcinoma: TX, N0, M0
Stage 0: TisN0M0
Stage IA: T1a,bN0M0
Stage IB: T2aN0M0
Stage IIA: T2bN0M0; T1a,bN1M0; T2aN1M0
Stage IIB: T2bN1M0; T3N0M0
Stage IIIA: T1a,b, T2a,b, N2M0; T3N1, N2M0; T4N0, N1M0
Stage IIIB: T4N2M0; any T N3M0
Stage IV: Any T any NM1

Reproduced from reference 42, by permission of Blackwell Publishing. *The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a. †T2 tumours with these features are classified T2a if 5 cm or less or if size cannot be determined, and T2b if greater than 5 cm but not larger than 7 cms. ‡Most pleural (pericardial) effusions with lung cancer are due to tumour; in a few patients, however, multiple microscopical examinations of pleural (pericardial) fluid are negative for tumour, and the fluid is non-bloody and is not an exudate; where these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient should be classified as M0.

chromosome FISH probes. Chromosomal aneusomy was identified within 18 months of diagnosis of lung cancer with a sensitivity of 76% and specificity of 88%.[35] Centrally located and squamous-cell cancers had a higher sensitivity of detection. Chromosomal aneusomy had an adjusted odds ratio of 29·9 for association with lung-cancer diagnosis within 18 months. Genomic changes in preinvasive bronchial biopsies were confirmed in another study[36] that used six FISH probes, two of which were different from those used by Varella-Garcia and colleagues.

Volatile organic compounds can be detected in exhaled breath and are being investigated for their ability to detect early lung cancers.[37] Mazzone and associates[37] used a colorimetric assay to assess exhaled breath and recorded a sensitivity of 73% and specificity of 72%. These results and those of others, with varying methods of exhaled breath detection, are promising, but clearly need further improvement. Urinary concentrations of tobacco-specific nitrosamine metabolites have been associated with as much as an eight times increased risk of lung cancer in smokers.[38]

Finally, there is abundant interest in development of risk models for prediction of lung cancer.[39] Such a model could result in a more cost-effective approach to lung-cancer screening. Irrespective of the results of the randomised CT screening trials, research into biomarkers for both predisposition and early detection is clearly alive and well. The next decade looks very exciting for early detection of lung cancer.

Prognostic factors

The assessment of prognosis is an important factor affecting the selection of appropriate treatment for each individual case. The variables that are associated with prognosis can be grouped into categories: tumour-related, such as primary site, cell type, and extent of disease; patient-related, such as performance status, comorbidity, and sex; and environmental factors, such as nutrition and the choice and quality of treatment.[40] These variables can be useful individually or combined to form a composite prognostic index. A full discussion of these factors is beyond the scope of this Seminar, which will focus on data that have become available since the previous *Lancet* Seminar on lung cancer.[1]

The anatomical extent of disease, as described by the TNM classification, is one of the most important prognostic factors in NSCLC and small-cell lung cancer.[41] The seventh edition of the TNM classification was published late in 2009, and came into effect from Jan 1, 2010 (panel 1).[42] Although there have been significant changes in some T and M descriptors (panel 2) and the resultant TNM stage groupings, the most significant change in this revision has been the process of revision itself. The changes incorporated into the seventh edition were entirely based on proposals formulated by the International Staging Project of the International Association for the Study of Lung Cancer (IASLC), derived from the analysis of the largest database ever accumulated for this purpose, with data contributed from 46 sources in more than 19 countries around the world and with information about patients treated by all modalities of care.[43–47]

In addition to the changes listed in panel 2, there are several other novel aspects of the seventh edition, including the inclusion of bronchopulmonary carcinoid tumours,[48] a definition of visceral pleural invasion,[49] clarification of the distinction between lung metastases and multiple synchronous primary tumours, and a new nodal chart that reconciles the differences between previous versions.[50] Detailed guidance is available in the IASLC Staging Manual in Thoracic Oncology.[51]

The IASLC staging project studied the effect of prognostic factors, in addition to the anatomical extent of disease, for which data were available in the international database. For cases of NSCLC for which prognostic factors were analysed by clinical stage,[52] using the seventh edition, histology cell type was a significant prognostic factor for survival only in patients with stage IIIA disease, whereas performance status, sex, and age were significant in all stages, but with a lower limit for age in advanced stages. In advanced stage IIIB or IV disease, for which there were laboratory test results for at least one of calcium, albumin, sodium, haemoglobin, and white blood cell count, an analysis compared the prognostic power of each test against age, sex, and performance status. The laboratory variables in advanced NSCLC seemed to be strong prognostic factors, with a magnitude similar to that of performance status, whereas age and sex were weaker. In patients for whom data were available for all five laboratory tests, a multivariate model identified performance status and white blood cell count as strong significant prognostic factors, followed by calcium, albumin, and age. For surgically managed and pathologically staged I–IIIA NSCLC,[53] age, sex, and to a lesser extent cell type, in addition to pathological TNM stage, are all prognostic factors. Stage remains the most important factor, followed by age, and in early-stage cases, sex.

A meta-analysis[54] has shown in a univariate analysis that the maximum standardised uptake value of the primary tumour on ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET scanning done at diagnosis is a strong prognostic factor. Although there have been thousands of reports about the role of molecular or biological markers in lung cancer, these have been limited to univariate analyses, and international validation using multivariate analyses in prospective studies is still needed. An up-to-date review[19] of those biomarkers showing most promise in the prognostic setting has also emphasised the importance of standardisation and validation of the techniques used, which were immunohistochemistry, gene expression, mutational analysis, and microarray.

The TNM classification has stood the test of time and remains the most powerful prognostic instrument in lung cancer.[53] A challenge for the future will be to integrate TNM with other prognostic factors to create a composite prognostic index for NSCLC.

Panel 2: **Changes to the TNM descriptors in the seventh edition of the TNM classification of lung cancer[42]**

- A new cutoff of 2 cm now divides T1 tumours into T1a 2 cm or less and T1b tumours larger than 2 cm but not more than 3 cm
- A new cutoff of 5 cm divides T2 tumours into T2a larger than 3 cm but not more than 5 cm and T2b tumours larger than 5 cm but not more than 7 cm
- A new cutoff of 7 cm was created, and tumours larger than 7 cm are classified as T3—size for the first time becoming a T3 descriptor
- Tumours associated with additional tumour nodules in the same lobe as the primary are reclassified from T4 to T3
- Tumours associated with additional tumour nodules in other ipsilateral lobe(s) are reclassified from M1 to T4
- Tumours associated with additional tumour nodules in the contralateral lung remain M1, but are reclassified as M1a
- Tumours associated with malignant pleural or pericardial effusion or pleural or pericardial nodules are reclassified from T4 to M1a
- Tumours associated with distant metastases are reclassified as M1b

Advances in surgical treatment

Technological advances and knowledge generated from clinical trials continue to improve our understanding of the role of surgery in staging, selection, and surgical management of patients with lung cancer. Mediastinoscopy and mediastinal lymph-node biopsy

was widely done for the diagnosis and staging of lung cancer, but with increasing availability and use of PET and PET/CT, mediastinoscopy became reserved to screening for false-positive results on PET so as not to deny suitable patients the option of surgery. One of the fastest developing areas is endobronchial and endoscopic ultrasound to obtain tissue diagnosis of lung cancer (via aspiration of proximal tumour or indirectly via aspiration of a mediastinal lymph node) and to stage the mediastinum with impressive sensitivity (88%) and specificity (100%).[55] As more centres acquire the technology and master the techniques, the need for mediastinoscopy is likely to decrease further. With a specificity of 100%, positive results of endobronchial and endoscopic ultrasound need no further confirmation, and role of surgical mediastinoscopy is likely to be used to confirm negative results of ultrasound aspiration biopsy, increasing the sensitivity of this joint approach to 94%.[56]

Technical improvements have led to the development of lung resection with video-assisted thoracoscopic access (VATS lung resection). Of the 21 comparative studies (two of which were randomised), a systematic review concluded that there were no differences in air leaks, arrhythmia, pneumonia, mortality, or local recurrence between resections done open or using VATS, but there were lower systemic recurrences and improved 5-year survival with VATS.[57] Since most studies were not randomised, the effect of case selection is difficult to ascertain. The lower rate of systemic recurrence might suggest an earlier stage of patients in the VATS group. A nationwide US survey of more than 13 000 patients reported conflicting results, with a 1·6-times increase in complications in patients who underwent VATS lung resection.[58] Current balance of risks and benefits suggest that thoracoscopic lung resection might be a viable option for selected patients with early-stage cancer, but further randomised trials are needed to improve definition of the risks, benefits, and long-term outcomes.

The effect of intraoperative lymph-node management has been studied in two trials. One trial reported improved overall survival in patients randomly assigned to systematic nodal dissection (as opposed to lymph-node sampling),[59] and the other (ACOSOG Z0030) reported no difference (in patients with N0 or N1 disease).[60] Although the importance of systematic nodal dissection continues to be assessed, no increase in adverse effects were reported in the ACOSOG Z0030 trial,[61] and the Union for International Cancer Control continue to emphasise the importance of surgical lymph-node staging by recommending at least six nodes or stations to be sampled and negative before pathological N0 status is conferred.[62]

There have been substantial advances in understanding of the role of surgery as part of multimodal management in patients with resectable primary tumours and mediastinal lymph-node disease. The IASLC staging project suggested the idea of zoning of the mediastinal lymph-node stations and reported that patients with single-zone N2 disease (a zone can contain more than one station) had the same survival as did patients with multizone N1 disease,[45] and these findings have led to questioning of the rationale of excluding all patients with N2 disease. Moreover, clinical trials of induction chemotherapy in patients with N2 disease suggest no difference in survival between suitable patients randomly assigned to surgery or further radiotherapy.[63–65] Recently, a multicentre randomised trial[66] reported that patients with N2 disease who received induction chemoradiotherapy and who were assigned to surgery had better 5-year progression-free survival than did those not assigned to surgery. In the surgical group, most early deaths occurred in patients who underwent pneumonectomy (exploratory analyses reported improved overall survival in patients who underwent lobectomy). The cause of the high death rate is uncertain, and could be attributable to small numbers and surgical expertise, since Weder and colleagues[67] report a very respectable 3% mortality rate in 176 patients who underwent pneumonectomy after induction chemotherapy or chemoradiotherapy in specialist thoracic surgical units. Currently, opinion is more in favour of surgery, as the likelihood of a lobectomy to achieve complete resection increases.

The management of patients with clinical N2 disease is currently as heterogeneous as the classification of N2 disease itself, since some clinicians do not favour surgery as part of multi-modality treatment, some have a more favourable attitude to surgery in view of the results of the aforementioned recent trials, and others adopt a middle-ground stance by offering surgery only to patients who respond to induction treatment. In a large randomised trial, Albain and colleagues[66] confirmed that 5-year overall survival is indeed best in patients with pathological N0 disease, but offered further insight by quantifying the difference in 5-year overall survival between N0 and N1–3 to be 17% (41% *vs* 24%) compared with 8% for patients who for whatever reason did not undergo surgery. Whether subselection of patients for surgery is appropriate now hinges on the question of whether a difference of 17% is clinically meaningful, important, and prohibitive. If this is not the case, surgery can be considered for all patients who remain suitable after induction treatment.

A detailed review of the evidence on lung function assessment by the British Thoracic Society Guidelines Committee has identified several shortcomings in the interpretation of risk profile in patients being considered for surgery.[68] In view of the poor evidence base, underpowered studies, and use of composite endpoints that restrict interpretation of the risk, the role of functional evaluation has been called into question and there has been a move away from conventional thresholds towards a gradient of risk that is discussed with and decided by the patient.[69] This paradigm shift allows increased patient involvement in the clinical decision

	n	Stage	Chemotherapy	5-year benefit (%)	Hazard ratio (95% CI)	p value
ALPI[73]	1209	I–IIIA	MVdP*	3%	0·96 (0·81–1·13)	0·589
IALT;[74] IALT[75]	1867	I–IIIA	VincaP or EP*	4%	0·86 (0·76–0·98) 0·91 (0·81–1·02)†	0·03
BLT[76]	381	I–IIIA	Platin-based*	–2% (2 years)	1·02 (0·77–1·35)	0·90
BR10[77]	482	IB–II	VnrP	15%	0·69 (0·52–0·91)	0·04
ANITA[78]	840	IB–IIIA	VnrP*	9%	0·8 (0·66–0·96)	0·017
LACE[79]	4584	I–IIIA	Cisplatin-based*	5%	0·89 (0·82–0·96)	0·004
IGR-MRC[81]	8147	I–IIIA	Cisplatin-based in 22 out of 30 trials	4%	–0·87 (0·81–0·93)	<0·0001

n=number of patients. MVdP=mitomycin/vindesine/cisplatin. VincaP=vinorelbine, vindesine, or vinblastine/cisplatin. EP=etoposide/cisplatin. VnrP=vinorelbine/cisplatin. *Optional adjuvant radiotherapy. †Updated data.

Table 1: **Recent randomised cisplatin-based adjuvant trials and meta-analyses**

process, and this change is hoped to lead to increased uptake of lung resection in patients who accept the high risks associated with poor lung function.

The options for management of patients with poor lung function have included bronchoplastic and angioplastic sleeve resections, where as much as possible of the normal lung is preserved, and sublobar (wedge resection or segmentectomy) is occasionally offered, when this treatment is suitable. With recent advances in stereotactic radiotherapy[70] and with the introduction of radiofrequency ablation,[71] patients with poor lung function who do not accept the risks of surgery can be offered a wider range of therapeutic modalities.

Improvements in diagnostic imaging and endoscopic techniques are likely to refine the role of surgery in diagnosis and staging of lung cancer. Current evidence supports an expansion in surgery as part of multimodality management of patients with N2 disease, and greater uptake in patients who are willing to accept higher risks. Patients who do not accept the risks of surgery have the option of non-surgical local ablative procedures or stereotactic radiotherapy.

Advances in chemotherapy in adjuvant, induction, and multimodal settings

Despite optimum surgical management, the 5-year survival rate of resected NSCLC ranges from 25% to 73% according to pathological stage. In a meta-analysis[72] published in 1995, a 13% reduction in the risk of death was reported, suggesting an absolute benefit of 5% at 5 years with adjuvant chemotherapy.[72] These results constituted the rationale for a new generation of randomised studies with platin-based regimens.[73–78]

The LACE meta-analysis[79] pooled 4584 patients accrued in five recent cisplatin-based adjuvant trials. It confirmed the benefit of adjuvant chemotherapy, with a 5·3% improvement of survival at 5 years (p=0·0043). Disease-free survival was also improved (5·2% at 5 years, p<0·0001). In terms of pathological stage, there was a negative effect of adjuvant chemotherapy for stage IA. The risk reduction was 8% for stage IB and 17% for stages II and III. Effect of chemotherapy did not vary according to age, sex, performance status, type of surgery, and histology. In parallel, the adjuvant UFT meta-analysis[80] also confirmed a significant advantage of the drug compared with control in 2003 Japanese patients (p<0·001). With a total of more than 10 000 patients, a recently updated meta-analysis of individual data[81] has confirmed the significant effect of postoperative chemotherapy, with or without postoperative radiotherapy, with an overall benefit of 4% at 5 years. Table 1 summarises these results. In the future, some tumour markers such as ERCC1,[82] RRM1,[83] MSH2,[84] β-tubulin,[85] or BRCA1[86] might have a predictive value for selection of patients who will benefit from adjuvant platin-based chemotherapy. Targeted agents and vaccine therapy are also being evaluated as an adjuvant treatment after resection of NSCLC. Randomised studies are ongoing.

Preoperative treatment with chemotherapy offers several advantages. For example, downstaging occurs in about 50% of cases, sometimes allowing a complete resection. Induction chemotherapy also allows a front-line attack of micrometastases. Additionally, the compliance with preoperative chemotherapy is around 90%, compared with 60–70% for postoperative chemotherapy.[87]

Several phase 2 trials were undertaken in the 1980s to evaluate the benefit of induction chemotherapy in stage I–III NSCLC. The radiological response rates in these trials ranged from 39% to 79%. Secondary surgical resection was generally feasible, and a complete pathological response was seen in some patients. In the mid-1990s, the impressive results of two randomised phase 3 trials of induction chemotherapy versus front-line surgery had an important effect on the medical community. Both trials recruited 60 stage IIIA patients and were interrupted after positive interim results were recorded. Only two published randomised phase 3 studies comparing front-line surgery with preoperative chemotherapy followed by surgery accrued the number of patients that were initially planned: a French study that included 373 patients,[88] and the Medical Research Council LU22 trial that included 519 patients.[87] Among other studies that are either unpublished or that ended prematurely because of insufficient accrual, the SWOG (S9900) accrued 354 patients (out of 600 planned).[89] None of these large randomised studies could demonstrate a significant advantage in favour of preoperative chemotherapy. No meta-analysis of individual patient data from preoperative chemotherapy trials has been done, and the only available analyses are based on abstracts and literature data. The most recent literature-based meta-analysis included 1507 patients.[87] A hazard ratio (HR) of 0·88 (CI 95% 0·76–1·01, p=0·07) was reported, which is equivalent to an absolute improvement in survival of 5% at 5 years. A comparison of preoperative versus postoperative therapy has been done in the NATCH trial,[90] which showed no significant difference between the two adjuvant approaches.

Rather than asking whether neoadjuvant or adjuvant chemotherapy should be preferred, the key issue might be to determine which patients should be treated with adjuvant or neoadjuvant therapy. The neoadjuvant approach offers a unique opportunity to test new drugs and to compare tumour characteristics before and after induction therapy. Development of molecular-based therapeutic strategies will certainly be one of the major challenges of the next few years. Several randomised adjuvant studies have recently been initiated in Europe and in America, and are based on the molecular characteristics of each patient's tumour.

The benefit obtained with radiotherapy and chemotherapy given sequentially in locally advanced inoperable NSCLC is small, but is significant and well established. Several randomised trials comparing radiotherapy and chemotherapy given sequentially or concomitantly have suggested an improved outcome when both modalities were given early and simultaneously. Auperin and colleagues[91] undertook a meta-analysis of individual patient data from published and unpublished randomised trials that compared radiotherapy alone and the same radiotherapy combined with concomitant cisplatin-based or carboplatin-based chemotherapy. The analysis was based on nine trials including 1764 patients. Median follow-up was 7·2 years. The HR for death in patients treated with radiochemotherapy compared with radiotherapy alone was 0·89 (95% CI 0·81–0·98; p=0·02), corresponding to an absolute benefit of chemotherapy of 4% at 2 years. There was some evidence of heterogeneity among trials, and sensitivity analyses did not lead to consistent results. The combination of platin with etoposide seemed to be more effective than platin alone. The available data are insufficient to accurately define the size of such a potential treatment benefit and the optimum schedule of chemotherapy in combination with radiotherapy.

Advances in systemic therapy for advanced disease

First-line treatment

Chemotherapy remains the mainstay of treatment for advanced stage IIIB and IV NSCLC (table 2).[92–98] A platinum-based doublet is recommended for fit patients, and single agents can be offered in elderly patients or poor performance subsets.[99,100] Selection of therapy was not based on histological subtype until recently, when the multitargeted antifolate agent pemetrexed was shown to be less active in patients with squamous cancers than in other types of disease; approval of this agent is now limited to cancers of non-squamous histology.[92] In the first-line setting, cisplatin/pemetrexed is superior to cisplatin/gemcitabine, although no interaction by histological subtype was shown in a trial that compared pemetrexed/carboplatin with gemcitabine/carboplatin.[92]

The addition of molecularly targeted agents to platinum-based doublets has been studied extensively in many clinical trials during the past decade, with few trials showing any additional benefit and often showing excess toxic effects. The only agent to contribute significantly to response rate and survival is the angiogenesis inhibitor bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF).[93,101] In a large randomised trial, the addition of bevacizumab to paclitaxel/carboplatin significantly increased overall survival and led to the approval of this agent for treatment of patients with cancers of non-squamous histology.[93] Interestingly, a similar trial did not show any survival benefit when bevacizumab was added to gemcitabine/cisplatin,[101] and for this reason, many oncologists feel that the benefit of bevacizumab is not justified in view of the potential for toxic effects and added cost. No other angiogenesis inhibitor, whether a monoclonal antibody or tyrosine kinase inhibitor (TKI) of the VEGF receptor has shown significant activity in this clinical setting.[101] Indeed, at least one VEGF TKI trial has reported worse outcomes and unacceptable toxic effects profiles when combined with chemotherapy.[101]

The only other molecularly targeted agent to have been evaluated extensively with chemotherapy for NSCLC is cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR). Although all trials showed increased response rates with cetuximab, most failed to confirm either a significant or clinically meaningful survival benefit.[102] For that reason, cetuximab has not been approved for treatment of NSCLC.

Many predictive and prognostic markers have been assessed in NSCLC, but until recently no single molecular marker has been shown to be useful for either patient selection or selection of specific drugs.[103,104] However, a large randomised trial comparing the EGFR TKI gefitinib with paclitaxel/carboplatin chemotherapy in Asian patients with adenocarcinoma and a light-smoking or never-smoking history clearly showed that patients with sensitising mutations in exons 19 or 21 of the *EGFR* tyrosine kinase domain derived significantly greater benefit from gefitinib therapy, whereas the opposite was true for patients with wild-type *EGFR* (interaction p<0·0001).[96] Similar results were reported from a Korean trial[105] that compared gefitinib with gemcitabine/cisplatin in the same patient population. Although the molecular analyses included only a subset of patients in these two trials, their results are consistent. On the basis of the superior response rate, longer progression-free survival, and better toxicity profile, these studies suggest that an EGFR TKI might be the treatment of choice for patients with sensitising mutations. This conclusion has been confirmed in a Japanese trial[106] that prospectively compared paclitaxel/carboplatin with gefitinib as first-line treatment in patients with sensitising mutations. The survival results from these trials are immature and have thus far been published only in abstract form, but preliminary results suggest that the progression-free survival benefits are likely to result in an overall survival

	Treatment groups	ORR	Survival	HR (95% CI)	p value
JMDB[92]					
First-line	Pem/P *vs* Gem/P	30·6% *vs* 28·2%	10·3 m *vs* 10·3 m	0·94 (0·84–1·05)	NI
Non-squamous	Pem/P *vs* Gem/P	..	11·8 m *vs* 10·4 m	0·81 (0·70–0·94)	0·01
Squamous	Pem/P *vs* Gem/P	..	9·4 m *vs* 10·8 m	1·23 (1·0–1·51)	0·05
ECOG 4599[93]					
First-line, non-squamous	CP/Bev *vs* CP	15% *vs* 35%	12·3 m *vs* 10·3 m	0·79	0·003
FLEX[94]					
First-line	Vin/P/Cetux *vs* Vin/P	36% *vs* 29%	11·3 m *vs* 10·1 m	0·87 (0·76–0·99)	0·044
JMEN[95]					
Maintenance	Pem *vs* placebo	..	13·0 m *vs* 10·9 m	0·79 (0·63–1·01)	0·06
Non-squamous	Pem *vs* placebo	..	15·5 m *vs* 10·3 m	0·70 (0·56–0·88)	0·002
Squamous	Pem *vs* placebo	..	9·9 m *vs* 10·8 m	1·07 (0·77–1·5)	0·68
IPASS[96]					
First-line, adenocarcinoma, in Asian patients, light smokers	CP *vs* gefitinib	32% *vs* 43%	5·8 m* *vs* 5·7 m*	0·74 (0·65–0·84)	<0·0001
EGFR mutation	CP *vs* gefitinib	47% *vs* 71%	..	0·48 (0·36–0·64)	<0·0001
EGFR wild-type	CP *vs* gefitinib	24% *vs* 1%	..	2·85 (2·05–3·98)	<0·0001
JMEI[92]					
Second-line	Pem *vs* Doc	9·1% *vs* 8·8%	8·3 m *vs* 7·9 m	0·99 (0·82–1·2)	NI
Non-squamous	Pem *vs* Doc	..	9·3 m *vs* 8·0 m	0·78 (0·61–1·0)	0·048
Squamous	Pem *vs* Doc	..	6·2 m *vs* 7·4 m	1·56 (1·08–2·26)	0·018
INTEREST[97]					
Second-line	Gefitinib *vs* Doc	9·1% *vs* 7·6%	7·6 m *vs* 8·0 m	1·02 (0·91–1·2)	NI
BR.21[98]					
Second-line and third-line	Erlotinib *vs* placebo	9% *vs* <1%	6·7 m *vs* 4·7 m	0·71 (0·58–0·85)	<0·0001

ORR=overall response rate. HR=hazard ratio. Pem=pemetrexed. CP=carboplatin/paclitaxel. Gem=gemcitabine. NI=met the prespecified non-inferiority boundary. Bev=bevacizumab. VIN=vinblastine. P=cisplatin. Cetux=cetuximab. Doc=docetaxel. *This was the only trial to present progression-free survival in the main publication.

Table 2: **Landmark clinical trials in advanced non-small-cell lung cancer, by setting**

benefit as well. Gefitinib is the first agent to be approved on the basis of a molecular test in NSCLC.

A small proportion of patients with NSCLC have EML4–ALK mutations. Interestingly, these mutations occur in the same patient population that also has a high frequency of *EGFR* sensitising mutations, but the two are almost never found together in the same tumour. Crizotinib, an oral TKI that targets MET and EML4–ALK, is particularly active in patients with this mutation, and prospective trials comparing crizotinib to chemotherapy in this population are ongoing.[107] At this time, *EGFR* mutation testing is essential for the selection of first-line treatment with EGFR TKIs rather than standard platinum-based chemotherapy. Some centres have elected to restrict this testing to patients with adenocarcinoma or other clinical characteristics that might predict the presence of a mutation. Should crizotinib be approved, testing for the EML4–ALK mutation also will be essential, but at the present time, this treatment remains experimental. There is no other validated molecular marker that is currently recommended.

All guidelines recommend no more than six cycles of first-line chemotherapy, mainly because of the toxic effects of continued platinum-based doublet therapy.[99,100] Recently, however, there has been renewed interest in assessment of maintenance treatment with single-agent chemotherapeutic agents or molecularly targeted agents.[108] The largest and most convincing trial[95] assessed the value of maintenance pemetrexed in patients with stable or responding NSCLC after four cycles of doublet chemotherapy. This study showed both a significant and a highly meaningful survival benefit for patients with non-squamous histology who received maintenance pemetrexed, and this agent is now approved for this indication. The role of the EGFR inhibitors erlotinib and gefitinib as maintenance treatment has also been evaluated in two randomised trials.[109,110] Both studies showed significant increases in progression-free survival, and maintenance erlotinib resulted in significantly increased overall survival in patients whose tumours expressed EGFR protein.[109] However, the benefit was small, with only a month's difference at the median. None the less, erlotinib has been approved as a maintenance treatment in the USA, but only in patients with stable disease (not responders) in Europe.

Second-line treatment and beyond

Currently, docetaxel, pemetrexed (non-squamous cancers only), and the EGFR TKIs erlotinib and gefitinib are approved for second-line treatment of NSCLC.[111] These agents have all been shown to extend survival and improve symptoms. Whether chemotherapy or an EGFR

TKI should be selected in the second-line clinical setting was studied in a large randomised trial[97] that compared second-line single-agent docetaxel to the EGFR TKI gefitinib. This trial showed non-inferiority for gefitinib, but molecular substudies suggest that in patients with *EGFR* activating mutations, the benefit from gefitinib is the greatest.[112] A similar trial comparing erlotinib with pemetrexed is ongoing, and the results are awaited. In a large randomised trial,[98] erlotinib was compared with placebo in the second-line and third-line setting for advanced NSCLC. Treatment with erlotinib was associated with significant extension of survival and delay in time to deterioration of symptoms. Patients treated after both one and two lines of previous chemotherapy derived a similar extent of survival benefit from erlotinib. A similar trial[113] comparing gefitinib with placebo in the second-line and third-line setting did not show significant survival increases in the overall population. However, significant benefits were seen in lifetime non-smokers and patients of Asian origin.[113]

Molecular substudies[114,115] from the above two randomised trials have shown that patients with high *EGFR* copy number and *EGFR* sensitising mutations derived numerically greater benefit, but significant interaction was not shown, and so in this end-stage setting (by contrast with the first-line setting), treatment is not restricted to patients with a particular *EGFR* gene profile.

With treatment of proven benefit in the first-line, second-line, and third-line settings, the evaluation of many new drugs for NSCLC is now occurring in patients who have had two lines of chemotherapy and an EGFR inhibitor. Vandetanib, a dual inhibitor of both VEGF and EGFR, did not significantly extend survival compared with placebo in the third-line or fourth-line setting.[101,102] However, other EGFR TKIs have been shown to be active after erlotinib or gefitinib and could have activity in patients whose tumours have resistance mutations.[102] Although some trials of these drugs are still ongoing, others have completed accrual, and results should be available soon.

Advances in radiotherapy

Radiotherapy has important roles in both curative and palliative treatment of NSCLC. An estimated 75% of patients with NSCLC might benefit from radiotherapy.[116] Recent advances in radiotherapy for NSCLC have been more strongly affected by developments in technology than by an improved understanding of the radiobiology of the disease.

Curative radiotherapy might be indicated in patients with good performance status (Eastern Cooperative Oncology Group status 0–1) and inoperable disease localised to the primary site, with or without regional lymph-node involvement (stages I–III). Precise definition of the cancer's anatomical extent is crucial for accurate placement and shaping of the radiotherapy beams. The use of ^{18}F-FDG PET/CT scanning in the radiotherapy treatment position allows for accurate definition of the gross tumour volume on the treatment-planning computer (figure 1).[117] Because of ventilatory and cardiac motion, many lung cancers move during and between treatments; if this movement is not accounted for, there is a risk of a geographic miss. The amount of intrafraction motion can now be recorded by four-dimensional CT,[118] which generates a composite image representing the tumour location thoughout the ventilatory cycle, so that appropriate allowance can be made in the volume to be treated. The problem of geographic miss due to interfraction motion has been addressed by the development of image-guided radiotherapy, which uses techniques to image soft tissues or implanted radio-opaque markers in the radiotherapy treatment room.[119] This technique enables localisation of the GTV immediately before treatment delivery so that positional adjustments can be made on a daily basis if the cancer has been displaced outside the treatment volume. Although various imaging devices exist (including CT scanners attached to the linear accelerator, or x-ray sources in the floor of the treatment room), there have been no direct clinical comparisons of their relative performance or effects on outcomes.

The increased precision and avoidance of radiosensitive critical organs that can be achieved with image-guided radiotherapy has encouraged some investigators to treat small gross tumour volumes with much higher doses

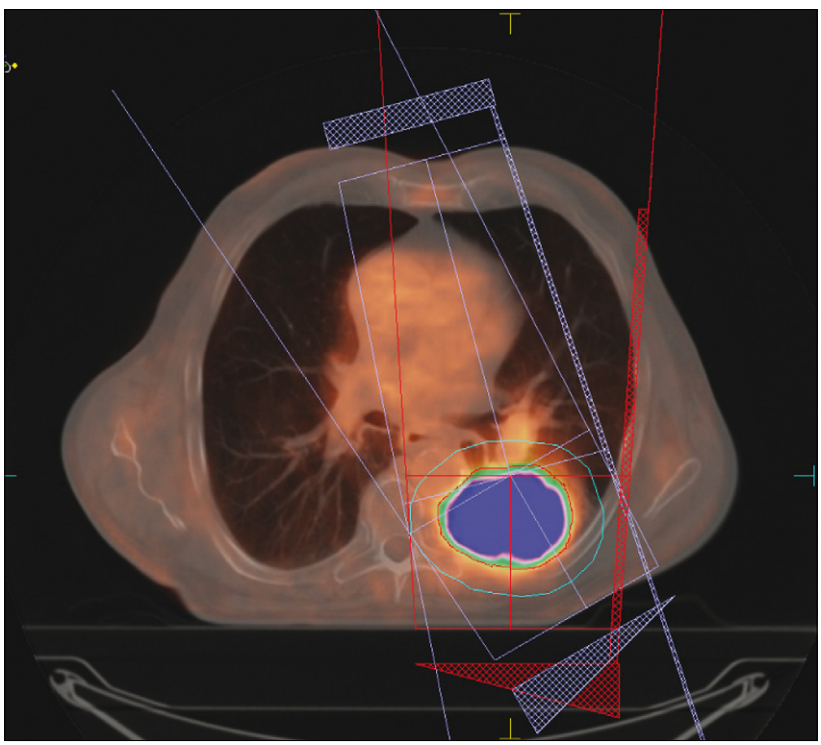


Figure 1: **A hybrid ^{18}F-FDG PET/CT scan displayed on the screen of a radiotherapy planning computer**
The FDG-avid tumour is clearly shown and has been outlined (gross tumour volume) on the screen. The three treatment beams arranged to avoid the spinal cord are also shown. Reproduced courtesy of Peter MacCallum Cancer Centre. FDG=fluorodeoxyglucose.

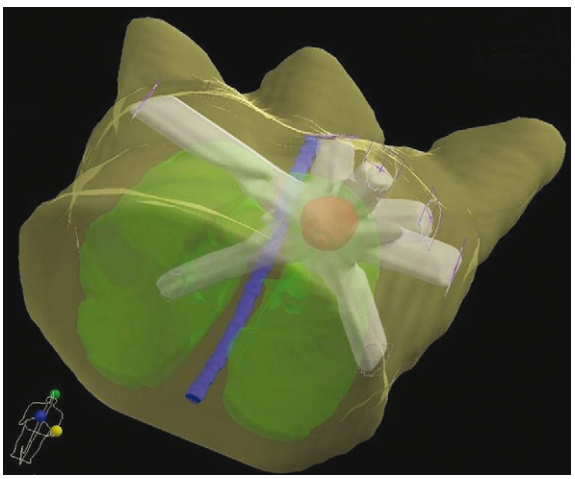


Figure 2: **Three-dimensional treatment plan for stereotactic radiotherapy showing several beams intersecting in the region of the tumour**
Beams are shown in white, the tumour in brown, the lungs in green, and the spinal cord in blue. Reproduced courtesy of Peter MacCallum Cancer Centre.

than were previously thought safe. The technique of using several (or dynamically arcing) radiation beams that only intersect at the locus of the cancer (figure 2), and giving a large total dose in five or fewer fractions (as opposed to 30 or more) has been termed stereotactic body radiotherapy (SBRT), although it is now more often image-guided rather than stereotactic. With this technique, high rates of local progression-free 2-year survival in the region of 90% have been observed in patients with stage I NSCLC.[120] This impressive effect on local control has led to a phase 3 trial comparing SBRT with surgery in operable peripheral stage I NSCLC.[121] Although the doses used in SBRT, for example 60 Gy in three fractions, do not seem excessive, because the dose per treatment (20 Gy) is large, the biological effect is much greater than the raw numbers would suggest, and an adjustment needs to be made to obtain the biological effective dose (BED).[122] In the example given, the BED of 60 Gy in three fractions is estimated to be 2·5-times larger than the BED of a conventional course of 60 Gy in 30 fractions. Serious toxic effects including fatalities have been reported after SBRT, particularly for centrally placed tumours,[123] which is not surprising in view of the high BED. No randomised trials comparing SBRT with other treatments have yet been reported, and further studies are required to standardise the treatment method and define its role in NSCLC.[120]

In patients with locally advanced stage IIIA and IIIB disease, conventionally fractionated radiotherapy concomitant with platinum-based chemotherapy (CRT) has emerged as the standard of care, since this treatment has been shown to improve local control and survival compared with either conventional radiotherapy alone or sequential chemotherapy followed by radiotherapy.[124] In a trial[66] involving patients with N2 NSCLC in which one of the groups received radiotherapy (61 Gy) and concomitant cisplatin and etoposide, the 5 year survival was 20%. Altered fractionation, in particular continuous hyperfractionated accelerated radiotherapy (CHART) given in 12 days instead of 42 days, has also been shown to improve local control and survival, even though the dose (54 Gy) was lower than in the control group (60 Gy).[125] This finding is consistent with the hypothesis that accelerated repopulation of tumour clonogens later in the course of treatment is a cause of treatment failure in some lung cancers.[126] CHART and CRT have not been directly compared, but the difficulties associated with giving treatment three times a day over 12 consecutive days has limited the implementation of CHART to a few sites in the UK.[127] Nevertheless, the CHART result should stimulate further research into altered fractionation and other potential methods of counteracting accelerated repopulation.

In an update[128] of a previous meta-analysis assessing the value of postoperative radiotherapy in patients with completely resected NSCLC, the detrimental effect of radiotherapy in stage I and II disease was confirmed. In patients with mediastinal node involvement, the effect is less clear, with two recent non-randomised studies[129,130] suggesting a survival benefit with radiotherapy. This question is now the subject of a European randomised trial, Lung ART.

Brain metastases are a common cause of morbidity and death in patients with NSCLC. In one randomised trial, the incidence of brain metastases was 18% at 12 months; this proportion was reduced to 7·7% by the use of prophylactic cranial irradiation, but with no improvement in survival.[131] In patients with an established brain metastasis, the addition of a stereotactic radiosurgery boost increases survival compared with whole-brain radiotherapy alone.[132]

Palliation of symptoms is a major indication for thoracic radiotherapy. Although this effect can be achieved with short courses and low doses, a systematic review found a survival benefit for high doses, but with increased toxic effects.[133]

Contributors
Each author contributed a section to the Seminar, as follows: advances in pathology (AGN); advances in early diagnosis (JRJ); prognostic factors (PG); advances in surgical treatment (EL); advances in chemotherapy in the adjuvant, induction, and multimodality settings (TLC); advances in systemic therapy for advanced disease (FAS); advances in radiotherapy (DB).

Conflicts of interest
PG has received lecture fees from Eli Lilly and consultancy fees from Portaero. DB has participated in advisory boards for Lilly Oncology and AstraZeneca, has received honoraria from Lilly Oncology, and has received travel expenses from AstraZeneca. JRJ has participated in advisory boards for Genentech and Oncimmune. TLC declares that he has no conflicts of interest. EL has received consultancy fees from Strategen and Abbott Molecular and speakers' fees from Roche. AGN has participated in advisory boards for AstraZeneca, GlaxoSmithKline, and Oncimmune. FAS has received honoraria and consultancy fees from Eli Lilly, AstraZeneca, Roche, Merck EMD Serono, and Pfizer.

References
1 Hoffman PC, Mauer AM, Vokes EE. Lung cancer. *Lancet* 2000; **355:** 479–85.

2 WHO. Tumours of the lung, pleura, thymus and heart. Lyon, France: IARC Press, 2004.

3 Travis WD, Rekhtman N, Riley GJ, et al. Pathologic diagnosis of advanced lung cancer based on small biopsies and cytology: a paradigm shift. *J Thorac Oncol* 2010; **5:** 411–14.

4 Travis WD, Brambilla E, Noguchi K, et al. The New IASLC/ATS/ERS International Multidisciplinary Lung Adenocarcinoma Classification. *J Thorac Oncol* 2011; **6:** 244–85.

5 Kargi A, Gurel D, Tuna B. The diagnostic value of TTF-1, CK 5/6, and p63 immunostaining in classification of lung carcinomas. *Appl Immunohistochem Mol Morphol* 2007; **15:** 415–20.

6 Wu M, Wang B, Gil J, et al. p63 and TTF-1 immunostaining. A useful marker panel for distinguishing small cell carcinoma of lung from poorly differentiated squamous cell carcinoma of lung. *Am J Clin Pathol* 2003; **119:** 696–702.

7 Nicholson AG, Gonzalez D, Shah P, et al. Refining the diagnosis and *EGFR* status of non-small cell carcinoma in biopsy and cytologic material, using a panel of mucin staining, TTF-1, cytokeratin 5/6, and P63, and *EGFR* mutation analysis. *J Thorac Oncol* 2010; **5:** 436–41.

8 Loo PS, Thomas SC, Nicolson MC, Fyfe MN, Kerr KM. Subtyping of undifferentiated non-small cell carcinomas in bronchial biopsy specimens. *J Thorac Oncol* 2010; **5:** 442–47.

9 Varlotto JM, Flickinger JC, Recht A, Nikolov MC, DeCamp MM. A comparison of survival and disease-specific survival in surgically resected, lymph node-positive bronchioloalveolar carcinoma versus nonsmall cell lung cancer: implications for adjuvant therapy. *Cancer* 2008; **112:** 1547–54.

10 Borczuk AC, Qian F, Kazeros A, et al. Invasive size is an independent predictor of survival in pulmonary adenocarcinoma. *Am J Surg Pathol* 2009; **33:** 462–69.

11 Makimoto Y, Nabeshima K, Iwasaki H, et al. Micropapillary pattern: a distinct pathological marker to subclassify tumours with a significantly poor prognosis within small peripheral lung adenocarcinoma (</=20 mm) with mixed bronchioloalveolar and invasive subtypes (Noguchi's type C tumours). *Histopathology* 2005; **46:** 677–84.

12 Sica G, Yoshizawa A, Sima CS, et al. A grading system of lung adenocarcinomas based on histologic pattern is predictive of disease recurrence in stage I tumors. *Am J Surg Pathol* 2010; **34:** 1155–62.

13 Motoi N, Szoke J, Riely GJ, et al. Lung adenocarcinoma: modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis. *Am J Surg Pathol* 2008; **32:** 810–27.

14 Finberg KE, Sequist LV, Joshi VA, et al. Mucinous differentiation correlates with absence of EGFR mutation and presence of KRAS mutation in lung adenocarcinomas with bronchioloalveolar features. *J Mol Diagn* 2007; **9:** 320–26.

15 Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009; **27:** 4247–53.

16 International Union Against Cancer. TNM classification of malignant tumours. 7th edn. New York, NY, USA: Wiley-Liss, 2009.

17 Yoshida J, Nagai K, Asamura H, et al. Visceral pleura invasion impact on non-small cell lung cancer patient survival: its implications for the forthcoming TNM staging based on a large-scale nation-wide database. *J Thorac Oncol* 2009; **4:** 959–63.

18 Girard N, Deshpande C, Lau C, et al. Comprehensive histologic assessment helps to differentiate multiple lung primary nonsmall cell carcinomas from metastases. *Am J Surg Pathol* 2009; **33:** 1752–64.

19 Coate LE, John T, Tsao MS, Shepherd FA. Molecular predictive and prognostic markers in non-small-cell lung cancer. *Lancet Oncol* 2009; **10:** 1001–10.

20 Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. *Lancet* 2003; **362:** 593–97.

21 Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. *Radiology* 2005; **235:** 259–65.

22 The International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006; **355:** 1763–71.

23 Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. *JAMA* 2007; **297:** 953–61.

24 Infante M, Cavuto S, Lutman F, et al, for the DANTE Study Group. A randomized study of lung cancer screening with spiral computed tomography. *Am J Respir Crit Care Med* 2009; **180:** 445–53.

25 Gohagan JK, Marcus PM, Fagerstrom RM, et al, for the Lung Screening Study Research Group. Final results of the lung screening study, a randomized feasibility study of spiral CT versus chest x-ray screening for lung cancer. *Lung Cancer* 2005; **47:** 9–15.

26 Blanchon T, Bréchot JM, Grenier PA, et al, for the "Dépiscan" Group. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). *Lung Cancer* 2007; **58:** 50–58.

27 van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009; **361:** 2221–29.

28 Thorgeirsson TE, Geller F, Sulem P, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature* 2008; **452:** 638–42.

29 Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature* 2008; **452:** 633–37.

30 Spira A, Beane JE, Shah V, et al. Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer. *Nat Med* 2007; **13:** 361–66.

31 Bloomquist T, Crawford EL, Mullins DA, et al. Pattern of antioxidant and DNA repair gene expression in normal airway epithelium associated with lung cancer diagnoses. *Cancer Res* 2009; **69:** 8629–35.

32 Yee J, Sadar MD, Sin DD, et al. Connective tissue-activating peptide III: a novel blood biomarker for early lung cancer detection. *J Clin Oncol* 2009; **27:** 2787–92.

33 Zhong L, Coe SP, Stromberg AJ, et al. Profiling tumor-associated antibodies for early detection of non-small cell lung cancer. *J Thorac Oncol* 2005; **1:** 513–19.

34 Qiu J, Choi G, Wang H, et al. Occurrence of autoantibodies to annexin I, 14-3-3 theta and LAMR1 in prediagnostic lung cancer sera. *J Clin Oncol* 2008; **26:** 5060–66.

35 Varella-Garcia M, Schulte AP, Wolf HJ, et al. Chromosomal aneusomy in sputum as detected by fluorescense in situ hybridization (FISH) predicts lung cancer incidence. *Cancer Prev Res* 2010; **3:** 447–53.

36 Massion PP, Zou Y, Uner H, et al. Recurrent genomic gains in preinvasive lesions as a biomarker of risk for lung cancer. *PLoS One* 2009; **4:** e5611.

37 Mazzone PJ. Analysis of volatile organic compounds in the exhaled breath for the diagnosis of lung cancer. *J Thorac Oncol* 2008; **3:** 774–80.

38 Yuan JM, Koh WP, Murphy SE, et al. Urinary levels of tobacco-specific nitrosamine metabolites in relation to lung cancer development in two prospective cohorts of cigarette smokers. *Cancer Res* 2009; **69:** 2990–95.

39 Spitz MR, Hong WK, Amos CI, et al. A risk model for prediction of lung cancer. *J Natl Cancer Inst* 2007; **99:** 715–26.

40 Gospodarowicz MK, O'Sullivan B, Sobin LH. Prognostic factors in cancer. 3rd edn. New Jersey, USA: Wiley-Liss, 2006.

41 Shepherd FA, Crowley J, Van Houtte P, et al. The IASLC Lung Cancer Staging Project: proposals regarding the clinical staging of small-cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007; **2:** 1067–77.

42 Sobin L, Gospodarowicz M, Wittekind C, eds. TNM classification of malignant tumours, 7th edn. Oxford, UK: Blackwell Publishing, 2010.

43 Goldstraw P, Crowley J, IASLC International Staging Project. The IASLC international staging project on lung cancer. *J Thorac Oncol* 2006; **1:** 281–86.

44 Rami-Porta R, Ball D, Crowley JJ, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007; **2:** 593–602.

45 Rusch VR, Crowley JJ, Giroux DJ, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the N descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007; **2:** 603–12.

46 Postmus PE, Brambilla E, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007; **2:** 686–93.

47 Goldstraw P, Crowley JJ, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the stage groupings in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007; **2:** 706–14.

48 Travis WD, Giroux DJ, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the inclusion of carcinoid tumours in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2008; **3:** 1213–23.

49 Travis WD, Brambilla E, Rami-Porta R, et al. Visceral pleural invasion: pathologic criteria and use of elastic stains: proposals for the 7th edition of the TNM classification for lung cancer. *J Thorac Oncol* 2008; **3:** 1384–90.

50 Rusch V, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009; **4:** 568–77.

51 Goldstraw P. IASLC staging manual in thoracic oncology. 1st edn. Florida, USA: EditorialRx Press, 2009.

52 Sculier JP, Chansky K, Crowley JJ, Van Meerbeeck J, Goldstraw P, IASLC International Staging Project. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease as expressed by the 6th edition of the TNM classification of malignant tumours and the proposals for the 7th edition. *J Thorac Oncol* 2008; **3:** 457–66.

53 Chansky K, Sculier JP, Crowley JJ, et al. The International Association for the Study of Lung Cancer Staging Project: prognostic factors and pathological TNM stage in surgically managed non-small cell lung cancer. *J Thorac Oncol* 2009; **4:** 792–801.

54 Berghmans T, Dusart M, Paesmans M, et al. Primary tumour standardized uptake value (SUV max) measured on fluorodeoxyglucose emission tomography (PDG-PET) is of prognostic value for survival in non-small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. *J Thorac Oncol* 2008; **3:** 6–12.

55 Adams K, Shah P, Edmonds L, Lim E. Endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. *Thorax* 2009; **64:** 757–62.

56 Tournoy KG, Dooms CA, Rintoul RC, et al. A randomized trial comparing endosonography followed by surgical staging versus surgical mediastinal staging alone in non-small cell lung cancer: The ASTER study. *J Clin Oncol* 2010; **28** (suppl)**:** 15s.

57 Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. *J Clin Oncol* 2009; **27:** 2553–62.

58 Gopaldas RR, Bakaeen FG, Dao TK, Walsh GL, Swisher SG, Chu D. Video-assisted thoracoscopic versus open thoracotomy lobectomy in a cohort of 13,619 patients. *Ann Thorac Surg* 2010; **89:** 1563–70.

59 Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer* 2002; **36:** 1–6.

60 Darling GE, Allen MS, Decker P, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in patients with N0 or N1 (less than hilar) non-small cell carcinoma: results of the ACOSOG Z0030 trial. American Association of Thoracic Surgery Annual Meeting; Toronto, Canada; May 1–5, 2010.

61 Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006; **81:** 1013–19.

62 Goldstraw P. International Association for the Study of Lung Cancer staging handbook in thoracic oncology. Florida, USA: Editorial Rx Press, 2009.

63 Johnstone DW, Byhardt RW, Ettinger D, Scott CB. Phase III study comparing chemotherapy and radiotherapy with preoperative chemotherapy and surgical resection in patients with non-small-cell lung cancer with spread to mediastinal lymph nodes (N2); final report of RTOG 89-01. Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 2002; **54:** 365–69.

64 Shepherd FA, Johnston MR, Payne D, et al. Randomized study of chemotherapy and surgery versus radiotherapy for stage IIIA non-small-cell lung cancer: a National Cancer Institute of Canada Clinical Trials Group Study. *Br J Cancer* 1998; **78:** 683–85.

65 van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007; **99:** 442–50.

66 Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009; **374:** 379–86.

67 Weder W, Collaud S, Eberhardt WE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 2010; **139:** 1424–30.

68 Lim E, Baldwin D, Beckles M, et al. Guidelines on the radical management of patients with lung cancer. *Thorax* 2010; **6** (suppl 3)**:** 1–27.

69 Lim E, Beckles M, Warburton C, Baldwin D. Cardiopulmonary exercise testing for the selection of patients undergoing surgery for lung cancer: friend or foe? *Thorax* 2010; **65:** 847–49.

70 Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009; **27:** 3290–96.

71 Simon CJ, Dupuy DE, DiPetrillo TA, et al. Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. *Radiology* 2007; **243:** 268–75.

72 Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995; **311:** 899–909.

73 Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell lung cancer. *J Natl Cancer Inst* 2003; **95:** 1453–61.

74 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:** 351–60.

75 Arriagada R, Dunant A, Pignon J-P, et al, Long-term results of the International Adjuvant Lung Cancer Trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. *J Clin Oncol* 2009, **28:** 35–42.

76 Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004; **26:** 173–82.

77 Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005; **352:** 2589–97.

78 Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006; **7:** 719–27.

79 Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol 2008*; **26:** 3552–59.

80 Kato H, Ichinose Y, Ohta M, et al; Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004; **350:** 1713–21.

81 Stewart LA, Burdett S, Tierney JF, Pignon J, on behalf of the NSCLC Collaborative Group. Surgery and adjuvant chemotherapy (CT) compared to surgery alone in non-small cell lung cancer (NSCLC): a meta-analysis using individual patient data (IPD) from randomized clinical trials (RCT). *J Clin Oncol* 2007; **25:** 7552.

82 Olaussen KA, Dunant A, Fouret P, et al, for the IALT Bio Investigators. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med* 2006; **355:** 983–91.

83 Zheng Z, Chen T, Li X, Haura E, Sharma A, Bepler G. DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer. *N Engl J Med* 2007; **356:** 800–08.

84 Kamal NS, Soria JC, Mendiboure J, et al. MutS homologue 2 and the long-term benefit of adjuvant chemotherapy in lung cancer. *Clin Cancer Res* 2010; **16:** 1206–15.

85 Seve P, Lai R, Ding K, et al. Class III β-tubulin expression and benefit from adjuvant cisplatin/vinorelbine chemotherapy in operable non-small cell lung cancer: analysis of NCIC JBR.10. *Clin Cancer Res* 2007; **13:** 994–99.

86 Rosell R, Skrzypski M, Jassem E, et al. BRCA1: a novel prognostic factor in resected non-small-cell lung cancer. *PLoS One* 2007; **2:** e1129.

87 Gilligan D, Nicolson M, Smith I, et al, on behalf of the trial collaborators. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet* 2007; **369:** 1929–37.

88 Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol* 2002; **20:** 247–53.

89 Pisters K, Vallieres E, Crowley JJ, et al. Surgery with or without preoperative Paclitaxel and Carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. *J Clin Oncol* 2010, **29:** 1843–49.

90 Felip E, Massuti B, Alonso G, et al. A phase II randomized trial of surgery alone, or preoperative paclitaxel/carboplatin (PC followed by surgery or surgery followed by adjuvant PC in early stage non-small cell lung cancer: NATCH follow-up data. 13th World Conference on Lung Cancer; San Francisco, CA, USA; July 31–Aug 4, 2009; abstr PRS 3.

91 Auperin A, Le Pechoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006; **17:** 473–83.

92 Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two phase III studies. *Oncologist* 2009; **14:** 253.

93 Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; **355:** 2542.

94 Pirker R, Pereira JR, Szczesna A, et al. cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet* 2009; **373:** 1497–98.

95 Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009; **374:** 1432–40.

96 Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; **361:** 947.

97 Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008; **372:** 1809–18.

98 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; **353:** 123.

99 Azzoli CG, Baker S Jr, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009; **27:** 6251.

100 Gridelli C, Ardizzoni A, Douillard J, et al. Recent issues in first-line treatment of advanced non-small-cell lung cancer: results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology. *Lung Cancer* 2010; **38:** 319.

101 Wheatley-Price P, Shepherd FA. Targeting angiogenesis in the treatment of lung cancer. *J Thorac Oncol* 2008; **3:** 1173.

102 Wheatley-Price P, Shepherd FA. Epidermal growth factor inhibitors in the treatment of lung cancer: reality and hopes. *Curr Opin Oncol* 2008; **20:** 162.

103 Shepherd FA, Rosell R. Weighing tumor biology in treatment decisions for patients with non-small cell lung cancer. *J Thorac Oncol* 2007; **2:** S68.

104 Coate LE, John T, Tsao MS, Shepherd FA. Molecular predictive and prognostic markers in non-small-cell lung cancer. *Lancet Oncol* 2009; **10:** 1001–10.

105 Lee JS, Park K, Sang WK, et al. A randomized phase III study of gefitinib (Iressa) versus standard chemotherapy versus standard gemcitabine plus cisplatin) as first-line treatment for never-smokers with advanced or metastatic adenocarcinoma of the lung. *J Thorac Oncol* 2009; **4** (suppl 9)**:** S283 (abstr PRS.4).

106 Inoue A, Kobayashi K, Maemondo M, et al. A randomized phase III study containing gefitinib with carboplatin plus paclitaxel for the first-line treatment of non-small cell lung cancer with sensitive EGFR mutations: MEJ002 study. *Eur J Cancer* 2009; **7:** 6 (abstr 9LBA).

107 Bang Y, Kwak EL, Shaw AT, et al. Clinical activity of the oral ALK inhibitor PF0231066 in ALK-positive patients with non-small cell lung cancer. *J Clin Oncol* 2010; **28** (suppl 15)**:** 6s (abstr 3).

108 Coate LE, Shepherd FA. Maintenance chemotherapy in advanced non-small cell lung cancer. *J Thorac Oncol* 2010; **5:** 723.

109 Cappuzzo F, Ciuleanu T, Stelmakh T, et al. Erlotinib as maintenance treatment in advanced non-small-lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010; **11:** 521–29.

110 Gaafar V, Surmount G, Scagliotti G, et al. A double-blind, randomized, placebo-controlled phase III intergroup study of gefitinib in patients with advanced NSCLC, non-progressing after first-line, platinum-based chemotherapy (EORTC 08021, ILP01/03). *J Clin Oncol* 2010; **28** (suppl 15S)**:** 542s (abstr 7518).

111 Gridelli C, Ardizzoni A, Ciardiello F, et al. Second-line treatment of non-small cell lung cancer. *J Thorac Oncol* 2008; **3:** 430.

112 Douillard JY, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized INTEREST trial. *J Clin Oncol* 2010; **28:** 744.

113 Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled multicentre study (Iressa Survival Evaluation in Lung cancer). *Lancet* 2005; **366:** 1527–37.

114 Zhu CQ, da Cunha Santos G, Ding K, et al. Role of KRAS and EGFR as biomarkers of response to erlotinib in national Cancer Institute of Canada Clinical Trials Group study BR.21. *J Clin Oncol* 2008; **26:** 4268.

115 Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006; **24:** 5034–42.

116 Delaney G, Barton M, Jacob S, Jalaludin B. A model for decision making for the use of radiotherapy in lung cancer. *Lancet Oncol* 2003; **4:** 120–28.

117 MacManus M, Nestle U, Rosenzweig KE, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. *Radiother Oncol* 2009; **91:** 85–94.

118 Keall PJ, Starkschall G, Shukla H, et al. Acquiring 4D thoracic CT scans using a multislice helical method. *Phys Med Biol* 2004; **49:** 2053–67.

119 Verellen D, Ridder MD, Linthout N, Tournel K, Soete G, Storme G. Innovations in image-guided radiotherapy. *Nat Rev Cancer* 2007; **7:** 949–60.

120 Brock J, Ashley S, Bedford J, Nioutsikou E, Partridge M, Brada M. Review of hypofractionated small volume radiotherapy for early-stage non-small cell lung cancer. *Clin Oncol* 2008; **20:** 666–76.

121 Hurkmans CW, Cuijpers JP, Lagerwaard FJ, et al. Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study. *Radiat Oncol* 2009; **4:** 1.

122 Fowler JF, Tome WA, Fenwick JD, Mehta MP. A challenge to traditional radiation oncology. *Int J Radiat Oncol Biol Phys* 2004; **60:** 1241–56.

123 Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; **24:** 4833–39.

124 Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28:** 2181–90.

125 Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol* 1999; **52:** 137–48.

126 Fowler JF, Chappell R. Non-small cell lung tumors repopulate rapidly during radiation therapy. *Int J Radiat Oncol Biol Phys* 2000; **46:** 516–17.

127 Din OS, Lester J, Cameron A, et al. Routine use of continuous, hyperfractionated, accelerated radiotherapy for non-small-cell lung cancer: a five-center experience. *Int J Radiat Oncol Biol Phys* 2008; **72:** 716–22.

128 Burdett S, Stewart L. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. *Lung Cancer* 2005; **47:** 81–83.

129 Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006; **24:** 2998–3006.

130 Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P, Mahe MA. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys* 2008; **72:** 695–701.

131 Bae K, Wong SJ, Sun A, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of Radiation Oncology Group study RTOG 0214. *J Clin Oncol* 2011; **29:** 272–78.

132 Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; **363:** 1665–72.

133 Fairchild A, Harris K, Barnes E, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. *J Clin Oncol* 2008; **26:** 4001–11.