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.

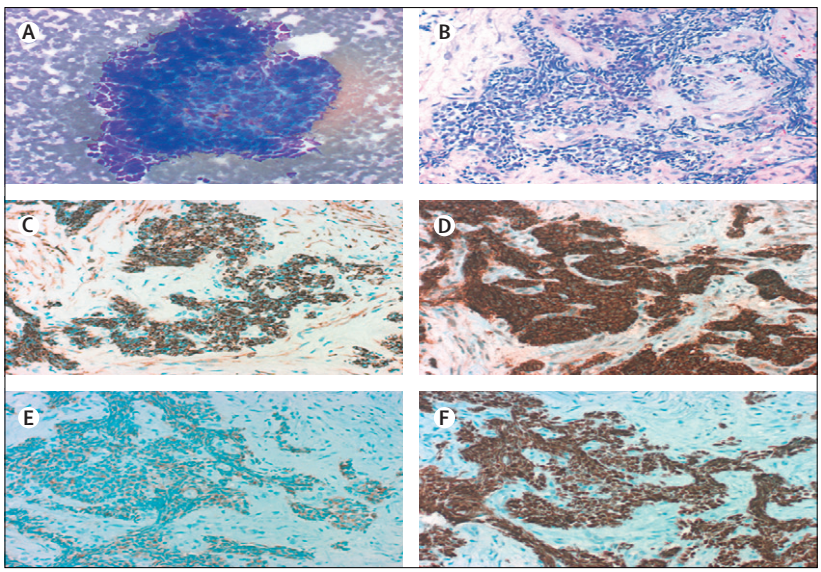

Figure 1: **Microscopic features of SCLC**
(A) In typical SCLC, cells are small (generally less than the size of three small resting lymphocytes) with scant cytoplasm, nuclear moulding, and finely granular nuclei with inconspicuous nucleoli (Diff-Quick staining, ×200). (B) Cells can be round, oval, or 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,

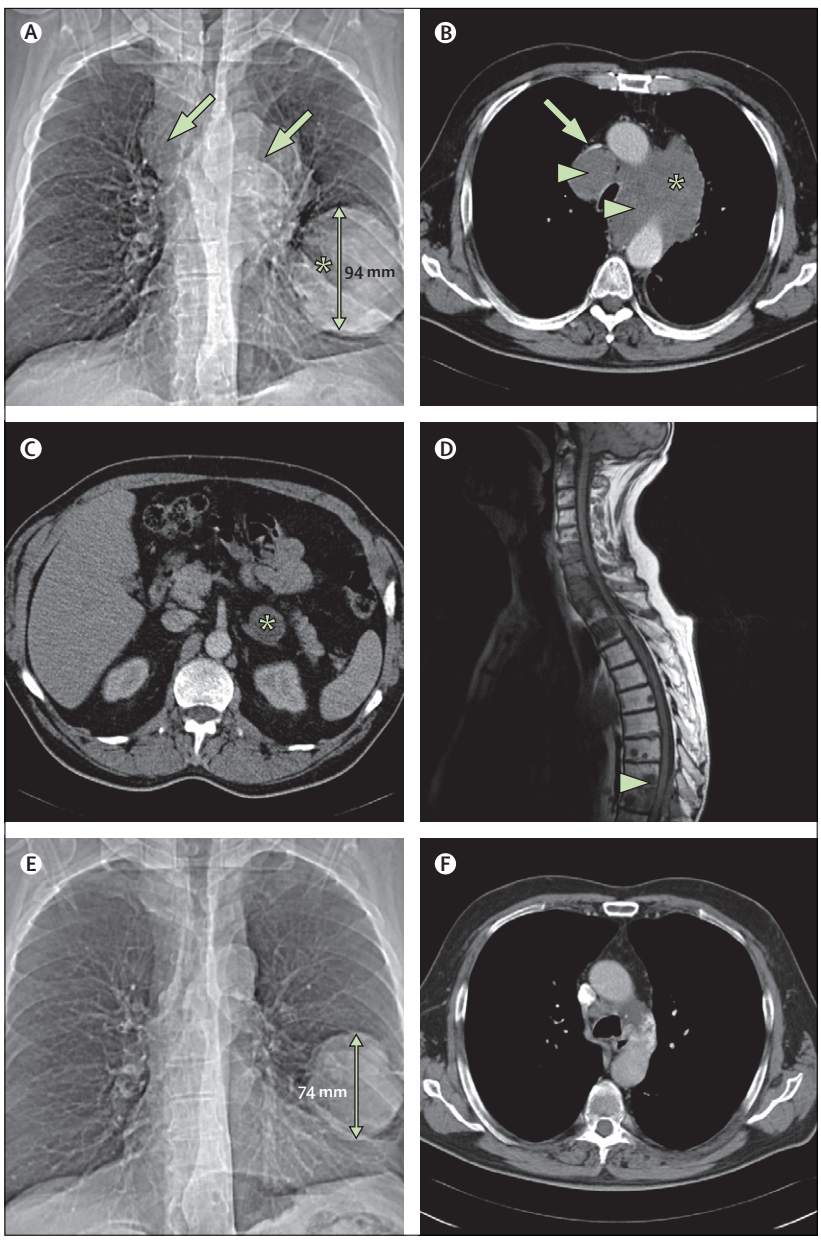

Figure 2: **Radiological imaging of SCLC at presentation and after treatment in a patient presenting with dyspnoea, stridor, and superior vena cava syndrome**
(A) Radiography showed a left lower lobe tumour (asterisk) with multiple enlarged mediastinal lymph nodes (arrows). (B) On CT the superior caval 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 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]

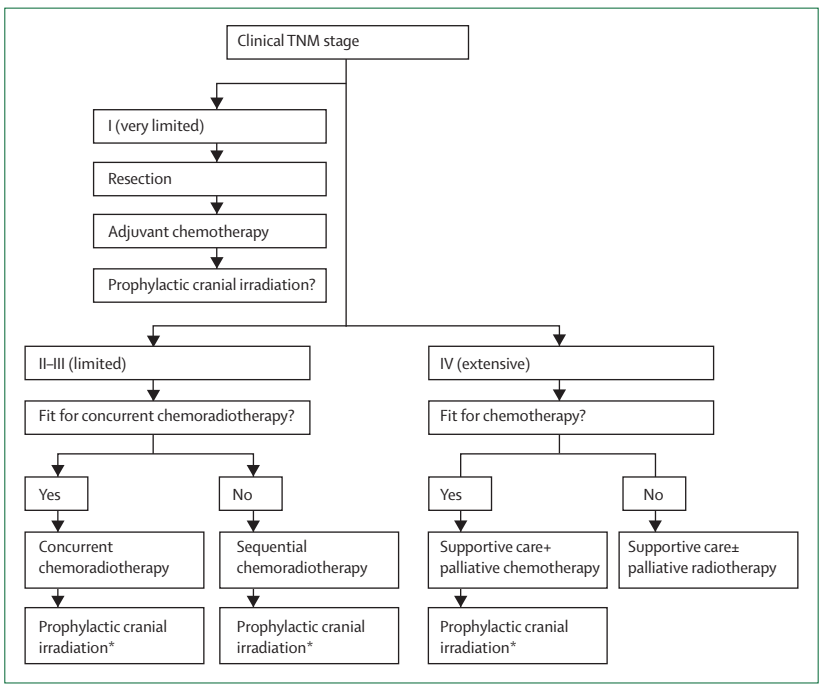

***Figure 3*: Simplified algorithm for the management of SCLC**
SCLC=small-cell lung cancer. *If not progressive after induction treatment

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

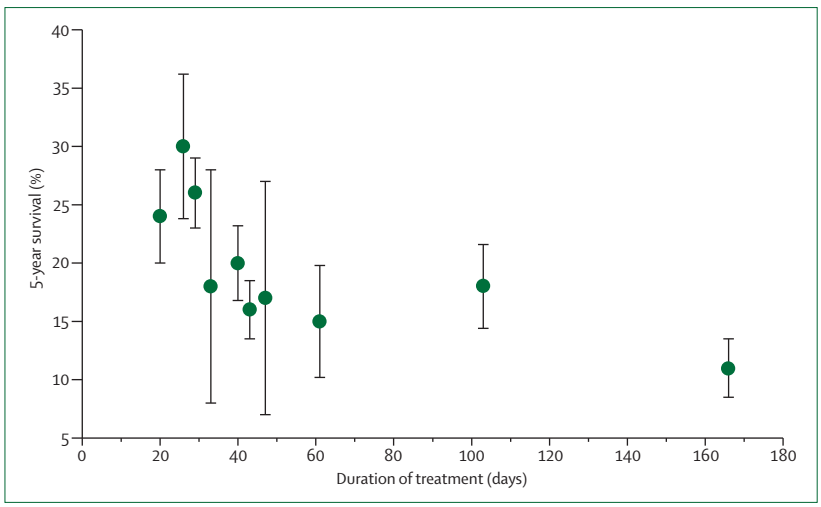

***Figure 4*: Survival at 5 years as a function of the time from the start of any treatment to the end of radiotherapy**
Each dot represents one trial with and error bars show SE. Reproduced from reference 96 by permission of the American Society of Clinical Oncology.

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]

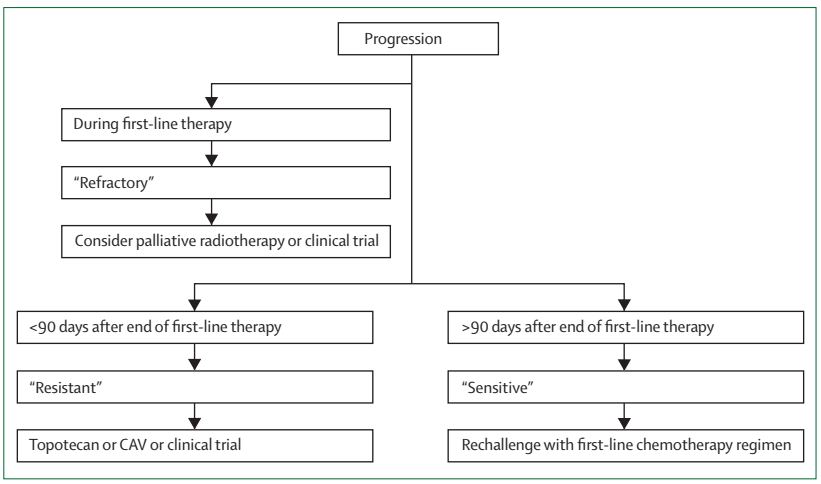

***Figure 5*: Simplified algorithm for the management of relapsing SCLC**
SCLC=small-cell lung cancer. CAV= cyclophosphamide, doxorubicin, and vincristine.

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

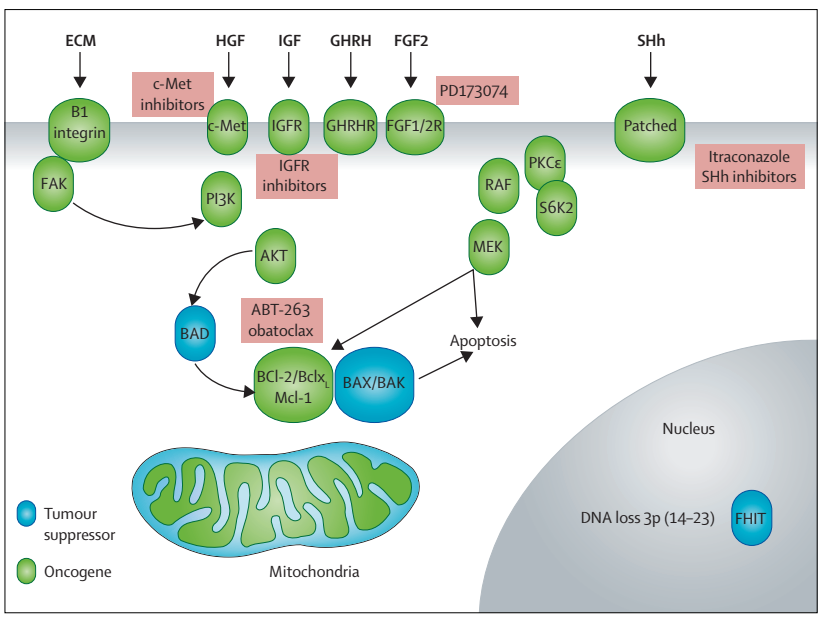

***Figure 6*: Suppression of apoptosis in SCLC cells and interaction with targeted agents**
SCLC cells can suppress apoptosis by increase in stimulation of antiapoptopic pathways via extracellular signals, by desensitisation of the intrinsic cell death machinery via addiction to antiapoptosis proteins, 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.