

MANAGEMENT OF SMALL CELL LUNG CANCER

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Small cell lung cancer initially was recognized as an entity distinct from other types of lung cancer in 1926 by Dr. Barnard. It commonly has been referred to as oat cell carcinoma because of its cytologic resemblance to grains of oats.⁸ The World Health Organization International Histologic Classification of Tumors has adopted the designation of small cell carcinoma rather than oat cell carcinoma.¹³⁸ The disease only rarely is treated successfully with surgery because small cell lung cancer typically is disseminated at the time of presentation.^{92, 93} The introduction of combination chemotherapy as treatment for this disease has resulted in high response rates and prolonged survival. The management of small cell lung cancer largely is based on systemic treatment with combination chemotherapy rather than surgical resection, which typically is used for non-small cell lung cancers.

Despite the high response rates, small cell lung cancer is fatal in 95% of the patients treated for this disease in the United States.²¹ This article focuses on recent advances in the management of small cell lung cancer, which include continued efforts to improve the results of systemic therapy, the use of effective combinations of chest radiotherapy with chemotherapy for patients with limited stage disease, and the use of prophylactic cranial irradiation.

DIAGNOSIS

Small cell lung cancer represents approximately 15% of the estimated 169,500 annual cases of lung cancer in 2001 in the United States, or approxi-

mately 25,000 patients.^{21, 42} More than 95% of patients with small cell lung cancer are current or past cigarette smokers, higher than other histologic types of lung cancer.^{15, 30} There is an increased risk with the increased numbers of cigarettes smoked per day and the duration of cigarette smoking.^{15, 57}

Patients with small cell lung cancer most commonly present with a submucosal endobronchial lesion and hilar enlargement on plain chest radiograph (Fig. 1).¹¹¹ The diagnosis typically is made by histologic analysis of bronchoscopic biopsy specimens or cytologic analysis of percutaneous and transbronchial fine-needle aspirations.^{19, 24, 52, 137} Small cell lung cancer is recognized as a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli.^{48, 138} The cells are round, oval, and spindle-shaped, and nuclear molding is prominent (Fig. 2). The mitotic rate is high. More than 90% of untreated small cell lung cancers are composed entirely of cells conforming to this morphologic description. The other recognized category includes combined small carcinoma, which is a small cell carcinoma combined with an additional component that consists of any of the histologic types of non-small cell carcinoma, usually adenocarcinoma, squamous cell carcinoma, or large cell carcinoma. Small cell carcinoma is less frequently combined with spindle cell or giant cell carcinoma. Further subtyping of small cell lung cancer beyond these two categories has not proved clinically useful.

The biopsy forceps can crush the biopsy specimen, and fine-needle aspiration also can distort the morphology of the cells, sometimes making it difficult to distinguish small cell lung cancer from

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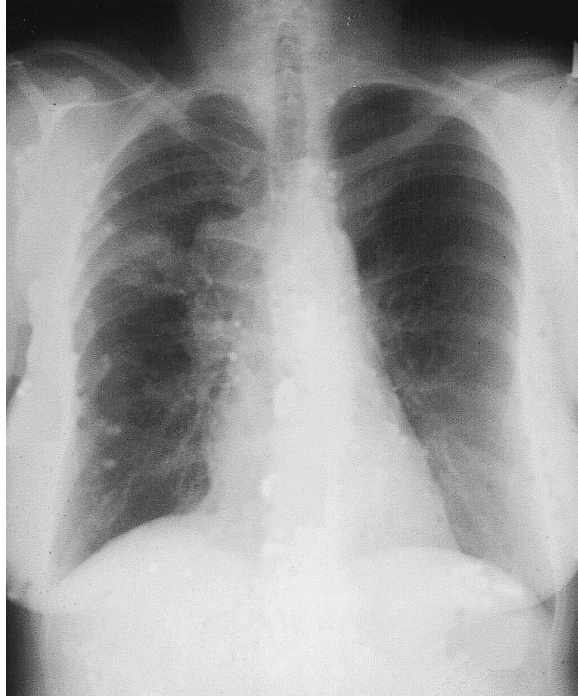


Figure 1. Chest radiograph from a patient with limited stage small cell lung cancer who presents with a right hilar lesion and mediastinal adenopathy.

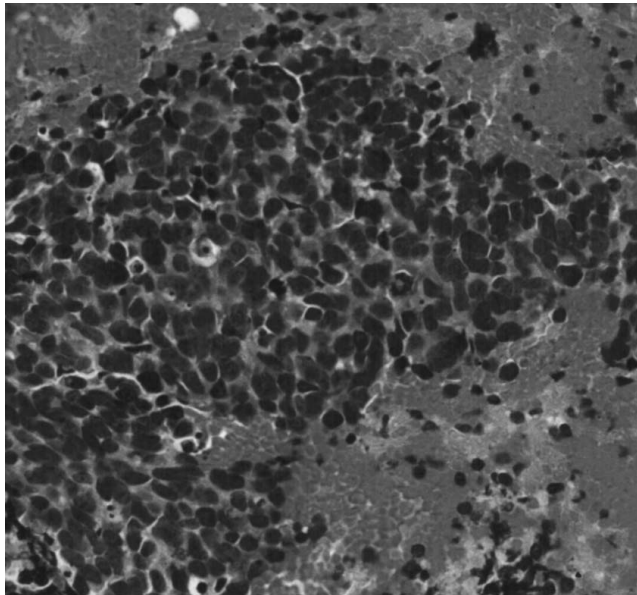


Figure 2. Photomicrograph of small cell lung cancer. The specimen is a diagnostic specimen from a patient with limited stage small cell lung cancer. The small cells are round or oval with scant cytoplasm, ill-defined borders, finely granular nuclear chromatin, and inconspicuous nucleoli with prominent nuclear molding ($\times 400$ hematoxylin-eosin stain). (Courtesy of R. Ilona Linnoila, M.D.)

Table 1. SYMPTOMS AND SIGNS OF PATIENTS PRESENTING WITH SMALL CELL LUNG CANCER

Symptom or Sign	(%)
Local	
Cough	50
Dyspnea	40
Chest pain	35
Hemoptysis	20
Hoarseness	10
Distant	
Weight loss	50
Weakness	40
Anorexia	30
Paraneoplastic syndromes	15
Fever	10

Data from Chute CG, Greenberg ER, Baron J, et al: Presenting conditions of 1539 populations-based lung cancer patients by cell type and stage in New Hampshire and Vermont. *Cancer* 56: 2107-2111, 1985.

non-small cell lung cancer. A pathologist experienced in reading pulmonary pathology should review the histologic and cytologic specimens to ensure diagnostic accuracy. Experienced pulmonary pathologists typically agree with the diagnosis of small cell versus non-small cell lung cancer more than 90% of the time.⁴⁹ If any question remains about the diagnosis, additional diagnostic material should be obtained. Patients present with local and distant signs and symptoms reflecting its origin in the lung and the systemic nature of the disease (Table 1).

PARANEOPLASTIC SYNDROMES

Compared with patients with other types of lung cancer, patients with small cell lung cancer more often have paraneoplastic syndromes. The well-characterized syndromes most frequently are mediated by production of peptide hormones or antibodies, and recent advances in molecular biology, peptide hormone characterization, and immunology have led to an increased understanding of some of these syndromes.

Hyponatremia of Malignancy

Patients with small cell lung cancer present with hyponatremia approximately 15% of the time, most commonly recognized as the syndrome of inappropriate antidiuretic hormone (SIADH).^{16, 61, 108} Ectopic production of arginine vasopressin causes hyponatremia and SIADH.^{10, 13, 16, 36, 44, 61} Atrial natriuretic peptide also plays a role in the regulation of sodium homeostasis in patients with small cell lung cancer. Atrial natriuretic peptide is produced ectopically in patients with small cell lung cancer.^{10, 16, 44} Patients with small cell lung cancer and hyponatremia, who do not have evidence of arginine vasopressin mRNA expression

or peptide production, produce atrial natriuretic peptide mRNA and peptide.^{44, 62} Elevations of plasma and tumor atrial natriuretic factor (ANF) have been identified in patients with hyponatremia.^{61, 70, 124} This peptide has been proposed to play a contributory role in the pathogenesis of hyponatremia in a few patients.

Cushing's Syndrome

This syndrome is clinically apparent in approximately 2% to 5% of patients with small cell lung cancer.^{1, 83, 119} The syndrome is mediated by the ectopic production of adrenocorticotrophic hormone (ACTH) by the lung cancer cells. The ACTH immunoreactivity in the plasma is present in more patients than those who have the syndrome. Stewart et al^{132, 133} showed that most small cell lung cancer cell lines secrete immunoreactive ACTH, but most of the immunoreactive material was ACTH precursors. There seems to be a defect in processing of the peptide hormone precursor proopiomelanocortin to mature ACTH, leading to immunoreactive protein without the biologic activity of ACTH.

Neurologic Paraneoplastic Syndromes

Multiple neurologic syndromes associated with small cell lung cancer seem to be mediated by antibodies directed against small cell lung cancer cells and neural tissue. The most common neurologic syndrome is Lambert-Eaton myasthenic syndrome and clinically is recognized by weakness and easy fatigability of proximal muscles.⁷⁶ The classic diagnostic electromyogram shows increasing amplitude of muscle action potentials with high-frequency stimulation.⁷⁶ The syndrome is associated with antibodies to voltage-gated calcium channels, which interfere with the release of acetylcholine, causing proximal muscle weakness.^{88, 122, 136, 147}

Cancer-associated retinopathy occurs predominantly in patients with small cell lung cancer. The syndrome is recognized clinically by rapid bilateral vision loss that can precede the clinical diagnosis of lung cancer.¹³⁵ In patients with small cell lung cancer, the syndrome is associated with antibodies in the serum that detect recoverin, a 23-kd protein present in retinal cells that also is produced in small cell lung cancer cells.^{84, 87, 105}

Small cell lung cancer also is associated with paraneoplastic encephalomyelitis and sensory neuropathy.^{22, 40, 41, 73, 86} More than 70% of the patients have multiple neurologic deficits that antedate the diagnosis of small cell lung cancer. Paraneoplastic encephalomyelitis and sensory neuropathy are caused by an antibody that reacts with a family of human neuronal RNA-binding proteins that also are made by small cell lung cancer cells. Patients with small cell lung cancer who have the antibody

Table 2. DEFINITION OF LIMITED AND EXTENSIVE STAGE FOR PATIENTS WITH SMALL CELL LUNG CANCER

Stage	(%)
Limited	30-40
Disease confined to one hemithorax with or without ipsilateral or contralateral mediastinal or supraclavicular lymph node metastasis and with or without ipsilateral pleural effusions independent of cytology	
Extensive	60-70
Any disease at sites beyond the definition of limited disease	

Data from Zelen M: Keynote address on biostatistics and data retrieval. *Cancer Chemother Biol Response Modif* 4:31-42, 1973.

present in their plasma live longer than patients who do not have the antibody.^{40, 73}

STAGING OF PATIENTS WITH SMALL CELL LUNG CANCER

The TNM staging system is not used typically for patients with small cell lung cancer because the patients usually do not undergo evaluation for surgical resection after the diagnosis is established. The staging classification for these patients is a simple, two-stage, Veterans Administration Lung Study Group system that categorizes patients as having limited or extensive stage disease.¹⁵⁰ The exact definition of *limited stage disease* can vary from institution to institution but typically is cancer limited to one hemithorax with hilar and mediastinal nodes encompassable in a tolerable radiotherapy portal (Table 2). Extensive stage disease is any disease beyond those boundaries.

The purpose of the staging evaluation is to identify potential metastatic sites of tumor involvement. The presence of sites of disseminated tumor influences the prognosis of the patient, directs the application of locoregional therapy, and permits assessment of tumor response to therapy. The symptoms and signs in patients with small cell lung cancer direct the evaluation to help identify metastatic sites (see Table 1). The most common sites of metastatic involvement at initial presentation are listed in Table 3. The initial evaluation is

Table 3. SITES OF METASTASES IN PATIENTS PRESENTING WITH SMALL CELL LUNG CANCER

Site	(%)
Liver	30
Bone	25
Bone marrow	20
Brain	10
Extrathoracic lymph nodes	5
Subcutaneous masses	5

directed at identifying patients with symptoms, signs, or laboratory values that predict a high likelihood of metastatic involvement.

Patients typically undergo a careful history, physical examination, and hematologic and serum chemistry examination. Patients routinely should have a chest radiograph and CT scan taken of the chest. These radiographic evaluations allow determination of the extent of intrathoracic involvement, including the potential presence of bilateral parenchymal disease, lobar collapse, extent of hilar and mediastinal involvement, and presence or absence of pleural fluid. The patients typically are diagnosed by fiberoptic bronchoscopy, which is abnormal in more than 90% of patients with small cell lung cancer.^{19, 53, 68, 137} This procedure also identifies the endobronchial extent of the tumor.

Patients with neurologic signs or symptoms should have MR imaging or CT scans done of the brain or MR imaging of the spinal cord because CNS metastases are identified in 80% to 90% of patients.^{50, 110} Patients with enlarged peripheral lymph nodes or subcutaneous masses should undergo needle aspiration or biopsy of the lesions because these histologically are involved more than 90% of the time.¹¹⁰ The patients should have their livers imaged by extending the CT scan of the chest through the liver. Further imaging with follow-up biopsy should be performed if this is the only potential site of metastatic disease.^{94, 102} Patients with abnormal complete blood count or peripheral blood smear should undergo bone marrow aspirate and a biopsy. Patients with brain metastases documented by MR imaging or cranial CT scan; histologic involvement of bone marrow, liver, and lymph nodes; or subcutaneous masses have documented involvement of small cell lung cancer outside of a tolerable radiotherapy portal and have extensive stage disease.

Staging Evaluation of Patients Participating in Clinical Trials or Treated with Locoregional Therapy

Patients who are considered for locoregional therapy (e.g., chest radiotherapy, surgical resection) or participation in clinical trials should undergo additional staging studies to identify asymptomatic metastatic sites. Patients should undergo imaging of the brain with MR imaging or CT scanning, a radionuclide bone scan with radiographs of abnormal areas, and imaging of the liver with CT scanning. Patients also may undergo bone marrow aspiration and biopsy, although there is not universal agreement on its use in staging patients with small cell lung cancer. The role of positron emission tomography for identifying metastatic sites in patients with small cell lung cancer is undergoing investigation but does not have a proved role in staging yet.^{47, 144} This more extensive staging evaluation allows a more thorough identification

of metastatic sites and spares the morbidity of chest radiation or surgery in patients who have asymptomatic metastatic cancer outside their chest. Except in a clinical trial with more rigorous staging requirements, patients who have an unequivocal site of metastatic tumor involvement that proves they have extensive stage disease can have their staging studies discontinued. The staging studies should be discontinued when a site is identified; the cost or the staging evaluation can be reduced by approximately 40%.¹¹⁰

In patients who have cancer confined to the chest, the staging information, CT scan of the chest, and pulmonary function tests should be reviewed with a radiation oncologist, and a determination should be made if they can tolerate chest radiotherapy. The patients are assigned a stage after staging and physiologic assessment has been completed (see Table 2). The proportion of patients with limited and extensive stage differ somewhat in various series, depending on the patient population and the extent of staging investigations used. The patients who undergo a more rigorous staging evaluation have more metastatic sites of disease identified; fewer have limited stage disease.

PROGNOSTIC FACTORS

Some of the following pretreatment characteristics of patients with small cell lung cancer consistently are associated with differences in the duration of survival*:

- Consistently Associated
 - Good performance status
 - Limited stage Disease
 - Female gender
 - Normal lactic dehydrogenase
- Inconsistently Associated
 - Normal serum sodium
 - Absence of a pleural effusion
 - Younger age
 - Absence of liver metastases
 - Absence of brain metastases
 - Normal liver function tests
 - Fewer sites of metastatic disease

The identification of factors associated with different outcomes allows physicians and investigators to compare different patient populations and interpret the contribution of treatment to differences in survival between different patient groups. An example of the importance of prognostic factors is the impact of gender on survival of patients with small cell lung cancer. The number of women developing lung cancer in the United States is increasing,⁴² and the proportion of women entering therapeutic trials has increased.^{23, 66, 131} These women also live longer than men.^{23, 66, 102, 131} The survival of patients participating in current trials

may be improving, in part, because of the increased percentage of women on the trial compared with those in the past, rather than an improvement in treatment.

CHEMOTHERAPY

The central therapeutic emphasis in patients with small cell lung cancer remains the use of combination chemotherapy. The most commonly used combinations of chemotherapy for patients with small cell lung cancer during the 1980s include etoposide and cisplatin (EP) or cyclophosphamide, doxorubicin, and vincristine (CAV) in doses and schedules similar to those listed in Table 4.^{29, 31, 54, 96, 140} The other agents commonly used in the United States documented to have single-agent activity against previously untreated ($\geq 20\%$ response rate) or treated ($\geq 10\%$ response rate) patients with small cell lung cancer include methotrexate, carboplatin, teniposide, ifosfamide, lomustine, paclitaxel, docetaxel, irinotecan, topotecan, vinorelbine, and gemcitabine.^{25, 39, 51, 74, 91}

The regimen in widespread use that provides consistent median survival times and modest toxicity is etoposide/cisplatin (EP). Etoposide/cisplatin largely has replaced the older CAV combination for patients with small cell lung cancer because of similar survival, decreased hematologic toxicity, and etoposide/cisplatin is combined easily with chest radiotherapy for patients with limited stage small cell lung cancer. (Fig. 3).^{34, 60, 112, 140, 141} The administration of etoposide/cisplatin plus chest radiotherapy for patients with limited stage disease should produce a complete response rate of 80% or more, a median survival of 18 months or more, and 5-year cancer-free survival of 20% to 25% of patients.^{11, 140} Patients with extensive stage disease should have a complete response rate of 20% or more, a median survival of 7 months or more, and 2% of patients achieve 5-year cancer-free survival.²¹ The death rate from complications of therapy should be less than 5%.

Table 4. CHEMOTHERAPY FOR SMALL CELL LUNG CANCER

Drug	Dosage and Schedule
EP*	
Etoposide	80–120 mg/m ² d 1, 2, and 3
Cisplatin	60–90 mg/m ² over 1 to 3 d
CAV	
Cyclophosphamide	1000 mg/m ²
Doxorubicin (Adriamycin)	50 mg/m ²
Vincristine	2 mg/m ²

*References 3, 23, 69, 72, 100, 102, 108, 113, 131, and 148.

*Administered intravenously every 3 wk. Data from references 29, 31, 54, 96, and 140.

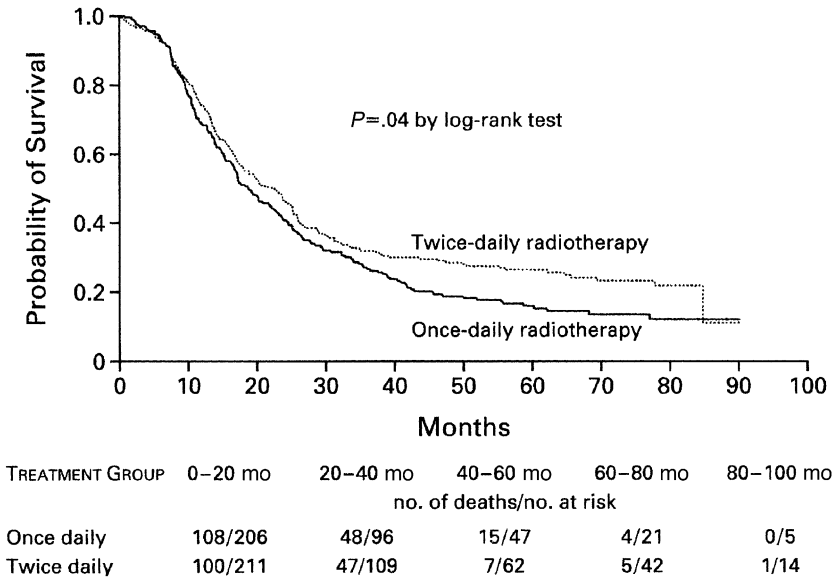


Figure 3. Kaplan-Meier estimates of survival for 417 patients treated with four cycles of etoposide and cisplatin with either twice-daily chest radiotherapy administered at 150 cGy per fraction twice daily or 180 cGy per fraction once daily to a total of 4500 cGy. The patients treated with twice-daily chest radiotherapy lived longer than patients treated with once-daily chest radiotherapy. (From Turrisi et al: *New Engl J Med* 340:265-271, 1999; with permission.)

STRATEGIES TO IMPROVE THERAPY FOR PATIENTS WITH SMALL CELL LUNG CANCER

Although most patients with small cell lung cancer achieve a partial or complete response, approximately 95% eventually die from the cancer.^{3, 21, 23, 78, 108} Clinical research has used multiple different strategies to improve the response rate and survival. These attempts have included systemic options using alternative chemotherapy regimens or local approaches using radiotherapy or surgical resection. The systemic approaches have included alternating chemotherapy combinations, administering more than two or three agents in combination, changing the schedule of etoposide administration, giving the chemotherapy weekly instead of every 3 to 4 weeks, shortening the treatment interval by adding cytokine support, increasing the doses of chemotherapy, or adding additional chemotherapy at the completion of four to eight cycles of chemotherapy (i.e., maintenance chemotherapy). Nearly all these approaches have not prolonged survival meaningfully or reduced the toxicity of the existing standard regimens. Several recent studies, however, show that patients treated with combination chemotherapy administered with shortened treatment interval or with more drugs live longer than patients treated with less chemotherapy.

Alternating Chemotherapy

The use of different alternating combinations of chemotherapy with each cycle for patients with small cell lung cancer has been investigated for many years. Several older studies showed longer survival when combinations including etoposide were alternated with cyclophosphamide-based regimens. A National Cancer Institute of Canada study that randomized 321 patients with extensive stage small cell lung cancer showed CAV alternating with EP was superior to CAV alone, with a prolongation of median survival 2 months ($P = 0.03$ for overall survival).²⁹ An Eastern Cooperative Oncology Group trial compared a CAV regimen with this regimen, alternating EP with a combination that included etoposide, with a prolongation of median survival of 1 month ($P = 0.002$ for overall survival).²⁸ In contrast, two studies of patients with small cell lung cancer from Japan and the United States, which enrolled a total of 777 patients, compared CAV and EP, alternating EP with CAV.^{34, 112} Both studies showed no difference in survival between the three arms (median survivals of 8-9 months; $P > 0.4$ for overall survival) in patients with extensive stage small cell lung cancer. Trials using alternating combinations of chemotherapy are not used commonly and are not a major focus of ongoing studies. The successful combination of chest radiotherapy with the combination of etoposide/cisplatin has made this combi-

nation the current standard of treatment for small cell lung cancer.^{11, 140}

Addition or Substitution of Drugs in the Standard Regimens

Multiple attempts have been made to modify the existing standard regimens by addition or substitution of drugs, including carboplatin, ifosfamide, cyclophosphamide, and an anthracycline. Some of these approaches have caused longer survival in patients with small cell lung cancer.

Carboplatin, Ifosfamide, Cyclophosphamide, and 4-Epidoxorubicin

The administration of cisplatin can cause severe nausea and vomiting and nephrotoxicity. Carboplatin has been substituted for cisplatin in the EP regimen in single-arm studies^{9, 128} and in two randomized studies that included more than 600 patients.^{77, 126} One study combined cisplatin or carboplatin with conventional doses of etoposide.¹²⁶ The second study combined either of these two drugs with combination with nine other drugs.⁷⁷ There was no significant difference in survival outcome between the arms of the studies. The current data show that there is no dramatic difference in outcome for patients treated with combination chemotherapy that includes cisplatin or the same regimen including carboplatin. There is more information about cisplatin, particularly when combined with chest radiotherapy, so the current standard regimens should include EP at doses similar to those listed in Table 4.

Two large, randomized studies have compared the standard regimen of etoposide plus cisplatin with the same drugs, adding ifosfamide (171 patients) or cyclophosphamide plus 4'-epidoxorubicin (226 patients).^{82, 107} Both of these regimens added alkylating agents (ifosfamide or cyclophosphamide) with or without an anthracycline (4'-epidoxorubicin). The patients treated with these three or four drug regimens lived longer than those who received the standard etoposide-cisplatin regimen. Further research is needed to determine if these more dose-intensive regimens increase the long-term survival of patients with limited or extensive stage small cell lung cancer, which likely will lead to more common use.⁵⁸

Etoposide Scheduling

Etoposide is among the most active agents used in combination chemotherapy regimens for pa-

tients with small cell lung cancer, and the schedule of administration affects its response rate and survival. The activity of etoposide has been assessed in different schedules, ranging from 1 to 21 days for patients with small cell lung cancer. Patients with limited and extensive stage disease treated with 3- to 5-day regimens of etoposide lived longer than patients treated on a single day.^{2, 18, 127} Seventy-eight patients with limited stage small cell lung cancer were randomized to be treated with doxorubicin and vincristine and 1 or 5 days of treatment with the same total dose of etoposide. The patients treated with the 5-day etoposide combination lived longer than patients treated with a single day ($P = 0.03$). Etoposide also has antitumor activity, using prolonged schedules of 14 to 21 days of therapy in phase II trials for patients with previously treated and untreated small cell lung cancer.^{26, 67, 95} These prolonged schedules of etoposide then were tested in randomized phase III trials. The 21-day regimen was compared with a 3-day regimen of etoposide combined with cisplatin for 306 patients with previously untreated extensive stage small cell lung cancer.⁹⁰ There was no survival advantage for the 21-day regimen. The 3- to 5-day regimen of etoposide was adopted as standard, and there is no obvious advantage for administering longer treatment durations of etoposide.

Weekly Administration of Chemotherapy

Treatment of patients with limited and extensive stage disease with weekly administration of chemotherapeutic agents for 9 to 16 weeks was reported by several groups.^{89, 98, 134} They typically include four to six different agents, and all these regimens include cisplatin, etoposide, and doxorubicin. Seventy-nine patients with limited stage disease had median survivals of 13 to 17 months, and 115 patients with extensive stage disease had median survivals of 10 to 14 months.^{89, 98, 134} The toxic death rates from these regimens were an acceptable 3%. Weekly chemotherapy has been compared with chemotherapy administered every 3 weeks in two randomized trials of 436 patients with extensive stage disease.^{35, 97} The median survival was similar for both arms, and more patients died on the weekly chemotherapy arm. Weekly chemotherapy has not been adopted as standard treatment for patients with small cell lung cancer.

Administration of Higher Doses of Chemotherapy

The high rate of systemic relapse has prompted attempts to improve the response rate and survival by using higher doses of chemotherapy. A small, older, randomized study of 90 patients with exten-

sive stage small cell lung cancer comparing a standard EP regimen with one with 67% higher doses shows no difference in survival between the two groups of patients.⁵⁴ A randomized study of 105 patients with limited stage disease showed patients treated with 25% to 33% initial higher doses of cisplatin or cyclophosphamide increased the survival at 2 years by more than 50%.⁶ Two phase II trials of 66 patients treated with autologous bone marrow transplantation achieved an encouraging 2-year survival in excess of 50% and 5-year survival of 40%.^{27, 32} There currently is no obvious dose-response documented for small cell lung cancer, however, so higher doses of chemotherapy are not used routinely but remain under investigation.

Duration of Chemotherapy Administration

The chemotherapy regimens should be given for 4 to 6 months, and therapy should be discontinued. Multiple randomized studies of maintenance chemotherapy for patients with small cell lung cancer have shown that chemotherapy treatment after the initial 4 to 6 months does not prolong survival.^{37, 116–118} Further chemotherapy can be reserved for relapse when and if it occurs. Patients who relapse 3 months or more after finishing their chemotherapy are threefold more likely to respond to subsequent chemotherapy.^{4, 103} This observation has been applied prospectively in a trial designed for patients with sensitive relapse small cell lung cancer. This trial showed 211 patients with previously treated small cell lung cancer have a similar response rate and live a similar period of time when treated with topotecan as a single agent compared with patients treated with vincristine, doxorubicin, and cyclophosphamide (Figure 4). The patients treated with topotecan had more relief of pulmonary and systemic symptoms than patients treated with vincristine, doxorubicin, and cyclophosphamide so it has been recommended as the second-line treatment.¹⁰³

Poor Performance Status Patients

Single-agent regimens with etoposide were developed as a more tolerable therapy to treat poor performance status patients with small cell lung cancer including elderly patients.^{12, 17} Single-agent regimens with etoposide were compared prospectively with combination regimens including etoposide plus vincristine or cisplatin and/or cyclophosphamide plus doxorubicin plus vincristine in 494 patients.^{38, 130} Patients treated with combination chemotherapy lived longer and had fewer side effects. Combination chemotherapy remains the standard treatment for patients with small cell lung cancer.

RADIOTHERAPY FOR PATIENTS WITH SMALL CELL LUNG CANCER

Chest Radiotherapy Combined with Chemotherapy for Patients with Limited Stage Small Cell Lung Cancer

The response rate of small cell lung cancer to chest radiotherapy as a single modality is approximately 75%.^{99, 114, 115} Chest irradiation effectively can control the cancer that presents in the chest and has cured a tiny fraction of patients with limited stage disease when used as a single modality.³³ The addition of chest radiotherapy to combination chemotherapy in treatment for patients with limited stage small cell lung cancer has been investigated in various chemotherapy and radiotherapy regimens.

A meta-analysis of 13 prospective randomized trials comparing chemotherapy with the same chemotherapy plus chest irradiation for patients with limited stage small cell lung cancer treated with combined modality showed 5% more patients alive at 2 and 3 years than patients treated with only chemotherapy.¹⁰⁴ Etoposide-cisplatin combined with twice-daily chest radiotherapy was introduced in the 1980s.^{60, 141} The patients had median survivals of nearly 2 years. The results of a trial comparing once- versus twice-daily chest radiotherapy combined with four cycles of etoposide plus cisplatin in 417 patients with limited stage small cell lung cancer recently have been reported (Fig. 3).¹⁴⁰ Patients treated with combined modality therapy, including twice-daily chest radiotherapy, lived longer than patients treated with once-daily so that more than 25% of patients were alive at 5 years. The current standard of treatment for limited stage disease is chemotherapy containing etoposide/cisplatin combined with concurrent twice-daily chest radiotherapy administered during the first or second cycle of chemotherapy.^{96, 140} Clinical research is ongoing to determine if higher doses of chest radiotherapy can be used rather than twice-daily chest radiotherapy.

Prophylactic Cranial Irradiation and Central Nervous System Toxicity

Patients who have been treated systemically for their small cell lung cancer successfully have a 50% to 67% risk for developing CNS metastases.^{5, 43, 60} Prophylactic cranial irradiation (i.e., irradiation administered in absence of evident metastases) typically in doses of 24 to 36 Gy given in 8 to 15 fractions has been used to prevent the development of brain metastases. Prophylactic cranial irradiation reduces the risk for brain metastases by 45% in patients who were randomized to receive prophylactic cranial irradiation compared with those who did not. A meta-analysis shows that 5% more patients are alive at 3 years when randomized to be treated with prophylactic cranial irradiation, compared with those not treated with pro-

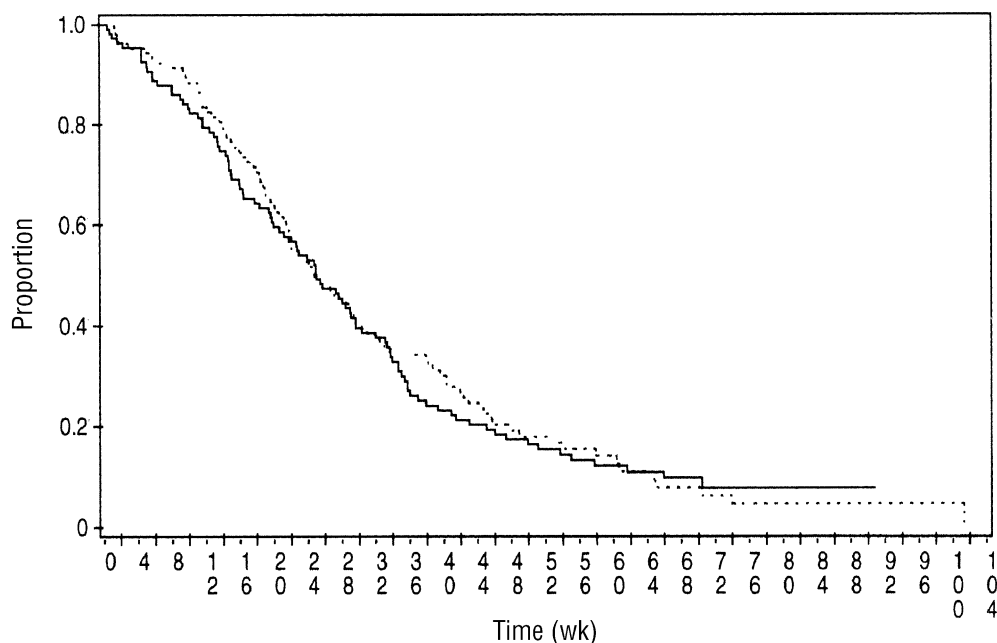


Figure 4. Kaplan-Meier estimates of survival for 211 patients with sensitive relapse small cell lung cancer treated with topotecan (*solid line*) versus cyclophosphamide, doxorubicin, and vincristine (*dotted line*). Patients assigned to treatment with topotecan lived a similar period of time as patients treated with cyclophosphamide, doxorubicin, and vincristine ($P = .772$). (From von Pawel et al: *J Clin Oncol* 17:658–667, 1999; with permission.)

phylactic cranial irradiation (Fig. 5).⁷ Despite concerns about impaired intellectual function in patients successfully treated for small cell lung cancer,^{65, 79, 81, 146} prospective studies have not confirmed these initial observations. The neuropsychologic testing showed that most impairment was present before administration of prophylactic cranial irradiation.⁷⁵ There also was no detectable difference in patients' neurologic function in those who randomly were assigned to be treated with prophylactic cranial irradiation, compared with those not treated.^{5, 43} Patients with small cell lung cancer achieving a complete remission should be treated with prophylactic cranial irradiation.

Radiotherapy for Patients with Extensive Stage Disease

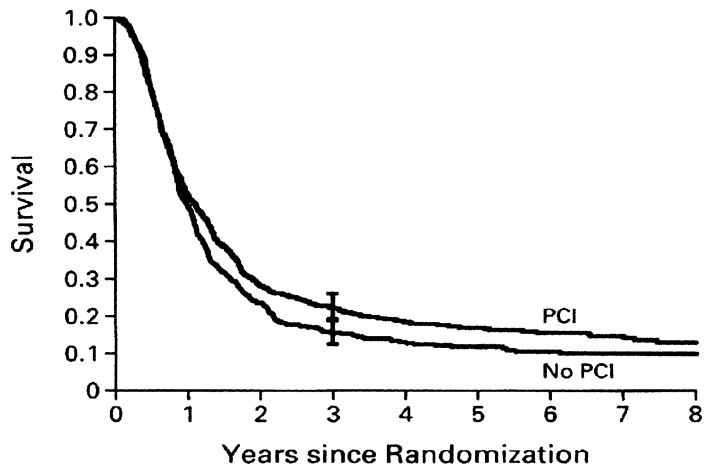
The role of radiotherapy for treatment of patients with small cell lung cancer who present with extrathoracic metastases is restricted to palliation of specific sites. Patients who present with symptomatic metastases to the brain detected by cranial imaging should undergo a course of cranial irradiation. The doses should be 30 to 40 Gy administered over 2 to 4 weeks. The systemic chemotherapy does not need to be delayed for the entire course of cranial irradiation. Cranial irradiation with greater than 30 to 40 Gy given over a period of time longer than 3 weeks or the use of stereotactic radiosur-

gery^{14, 80} can be considered for patients who have cranial metastases detected as their only sites of extrathoracic disease. These higher doses have not been proved to be of clinical benefit compared with more conventional doses. Although the administration of systemic chemotherapy reduces the size of some brain metastases,^{45, 85, 106} its role as a solitary treatment of brain metastases has not been established, so cranial irradiation should be used routinely for brain metastases.

Patients who present with painful bony metastases, impending bone fracture, or spinal cord compression are appropriate candidates for palliative courses of radiation. The radiation often is given in a dosage of 30 Gy over 2 weeks. Patients who fail to respond to chemotherapy can be treated with palliative courses of radiation for lobar collapse or superior vena cava syndrome. Patients with small cell lung cancer who present with superior vena cava syndrome or lobar atelectasis and have not received any treatment can be treated effectively with systemic combination chemotherapy and do not need chest irradiation.^{142, 143, 149} The routine administration of chest radiotherapy to patients with extensive stage small cell lung cancer has not been shown to prolong survival.

SURGERY FOR PATIENTS WITH SMALL CELL LUNG CANCER

Surgery was abandoned as routine treatment for patients with early stage small cell lung cancer



NUMBER AT RISK

No PCI	461	224	103	61	44	34	23	19	15
PCI	526	276	139	101	66	52	40	29	17

Figure 5. Kaplan-Meier estimates of survival for 987 patients with small cell lung cancer in complete remission assigned to treatment with prophylactic cranial irradiation versus patients not treated. The I bars denote the 95% confidence intervals. Patients assigned to prophylactic cranial irradiation lived longer than patients not assigned to prophylactic cranial irradiation ($P = .01$). (From Auperin et al: *New Engl J Med* 341:476–484, 1999; with permission.)

(clinical stage I, II, and IIIA) during the 1970s because fewer than 5% of patients were alive at 5 years.^{33, 92} In the 1980s, however, multiple retrospective series of patients who had surgical resection of early stage small cell lung cancer (pathologic stage I, II, and III) had 5-year survivals of approximately 20%.^{123, 125, 129} Patients with operable small cell lung cancer treated with surgery combined with chemotherapy or chest radiotherapy have a better 5-year survival (35%–40%).^{46, 71, 101, 109, 120} This observation has rekindled an interest in looking at the potential role of managing patients with isolated pulmonary nodules by surgery and chemotherapy. There is, however, no definitive evidence to date that suggests that surgical excision of small cell lung cancer contributes to this prolonged duration of survival in patients. Patients able to have their small cell lung cancer resected survive a similar period of time as patients without radiographic evidence of mediastinal involvement.¹²¹

The encouraging survival in patients with clinical stage I and II small cell lung cancer provides support for evaluating these patients for potential surgical resection. The patients should undergo surgical staging analogous to the approach for non-small cell lung cancer, including mediastinoscopy.^{55, 56} Ten percent of patients with normal-appearing mediastinal lymph nodes by CT scan have small cell lung cancer in their mediastinal lymph nodes. The existing evidence shows that patients who have been resected successfully should be treated with chemotherapy with or without chest irradiation. The definitive role of surgery for pa-

tients with small cell lung cancer, however, is under investigation.

LONG-TERM SURVIVAL OF PATIENTS WITH SMALL CELL LUNG CANCER TREATED WITH COMBINATION CHEMOTHERAPY

Experience with combination chemotherapy for patients with small cell lung cancer dates back more than 15 years, and there now are data that show that a few patients can be cured (Table 5). The risk for relapse from small cell lung cancer declines, so patients have a low risk for recurrence of small cell lung cancer after 5 years.^{59, 64, 78, 139} The overall mortality of patients surviving after successful treatment with chemotherapy, however, is still tenfold greater than an age-matched population, largely because of smoking-related second primary cancers.^{59, 78, 139}

Second Tumors in Long-term Survivors

A large percentage of the increased mortality in patients surviving after successful treatment for small cell lung cancer is caused by the development of other smoking-related malignancies (predominantly non-small cell lung cancer).^{59, 78, 139, 145} The chronic cigarette smoking that led to the initial small cell lung cancer places these patients at increased risk for aerodigestive tumors, which in-

Table 5. PATIENTS WITH SMALL CELL LUNG CANCER SURVIVING 5 YEARS OR LONGER

	Limited stage N (%)	Extensive stage N (%)	Overall N (%)
Johnson et al ⁶³	17/103 (17)	4/149 (3)	21/252 (8)
Paesmans et al ¹⁰²	10/365 (3)	4/398 (1)	14/763 (2)
Chute et al (SEER data) ²¹	(12)	(2)	(5)

SEER = Surveillance, Epidemiology, and End Results.

clude cancer of the lung, head and neck, and esophagus. The rate of developing second lung cancers in patients after surviving 2 years cancer-free is approximately 2% to 10% per patient per year, approximately 10 times the risk of adult male smokers who have not developed lung cancer.^{59, 139, 145} New lung masses occurring in patients successfully treated for small cell lung cancer may be surgically resectable non-small cell lung cancer.⁵⁹ Biopsies should be taken of the lesions, and if histologic examination shows non-small cell lung cancer, the patients should be evaluated for potential surgical resection of the lesion.

SUMMARY

Small cell lung carcinoma typically presents as a central endobronchial lesion in chronic cigarette smokers with hilar enlargement and disseminated disease. The diagnostic pathology should be reviewed by a pathologist accomplished in reading pulmonary pathology, and, if any doubt exists in the diagnosis, additional special stains or diagnostic material should be obtained. Patients with extensive stage disease should be managed by combination chemotherapy, whereas patients with limited stage disease should be treated with etoposide/cisplatin plus concurrent chest irradiation. The chemotherapy should be administered for 4 to 6 months and then should be discontinued. Prophylactic cranial irradiation should be given to patients who achieve a complete remission. Patients should be retreated with chemotherapy if they develop a relapse of their small cell lung cancer. The patients who are followed in complete remission should be observed carefully for second cancers, and appropriate therapy should be administered if the cancer reappears.

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