CHAPTER

43 Small Cell Lung Cancer

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INCIDENCE

Approximately 30,000 Americans are diagnosed with small cell lung cancer (SCLC) each year. This represents 13% to 15% of all cases of bronchogenic carcinoma.

BIOLOGIC CHARACTERISTICS

The 2004 World Health Organization (WHO) classification system describes two variants: small cell carcinoma and combined small cell carcinoma. The latter includes SCLC cells with any of the histologic types of non–small cell lung cancer (NSCLC).

STAGING EVALUATION

The International Association for the Study of Lung Cancer (IASLC) TNM Staging System is recommended for use in staging SCLC, but the 1973 Veterans Administration (VA) distinction of extensive stage (E-SCLC) compared to limited stage (L-SCLC) is commonly employed. Imaging studies including whole body 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/computed tomography (CT) and brain magnetic resonance imaging (MRI) should be routinely obtained if possible.

PRIMARY THERAPY, ADJUVANT THERAPY, AND LOCALLY ADVANCED DISEASE AND PALLIATION

Chemotherapy is standard therapy for all patients with SCLC who are fit enough to tolerate its use and etoposide with cisplatin (EP) are the most commonly used agents in the United States. The standard management of L-SCLC disease is EP given concurrently with thoracic radiation therapy (TRT). A Phase III trial demonstrated a survival advantage for twice-daily TRT over standard once-daily TRT. Fit patients with L-SCLC should undergo combined-modality therapy including twice-daily TRT to 45 Gy with concurrent EP for four cycles. Most current clinical protocols for L-SCLC employ the involved-field technique of TRT, in which the target volume includes the known extent of the primary tumor and malignant lymphadenopathy (as defined with CT and FDG-PET imaging). Elective radiotherapy (RT) of the supraclavicular and contralateral hilum is discouraged. If a patient achieves any degree of favorable response on restaging, prophylactic cranial irradiation (PCI) should be recommended. For patients with E-SCLC, primary therapy consists of EP and irradiation for symptomatic or nonresponding sites. Carefully selected patients with E-SCLC (with complete responses outside of the chest) should receive TRT. Following chemotherapy, PCI should be offered to all patients having any degree of response. Although long-term survival with E-SCLC is quite uncommon, about one fourth of patients with L-SCLC will survive 5 years or longer.

INTRODUCTION

During 2013, lung cancer was diagnosed in an estimated 246,210 patients and caused an estimated 163,890 deaths in the United States.[1] Between 13% and 15% of patients with lung cancer have SCLC, and of these, about 30% have L-SCLC.[2] Few patients with SCLC have stage I disease. Lung cancer occurs quite frequently in the elderly with a median age of 71 years at diagnosis.[3]

The natural history of untreated SCLC included rapid tumor progression with a median survival of only 2 to 4 months.[4] Until the late 1960s, physicians did not differentiate the management of SCLC from non-SCLC (NSCLC), and clinical trials in the 1970s continued to include both major histological types. It was recognized that most patients with SCLC had poor survival following resection or TRT with little apparent survival benefit from either. A major change in management occurred in the late 1960s and was linked to the recognition that SCLC was more responsive to chemotherapy than NSCLC.[5]

ETIOLOGY AND EPIDEMIOLOGY

The most common cause of SCLC is tobacco smoking. Additionally, secondary exposures to tobacco smoke and inhalation of asbestos or radon have also been associated with the development of this disease. Radon gas is the daughter product of decay of uranium and is most commonly found in areas with uranium within the soil.

Prevention and Early Detection

Prevention of SCLC is possible by addressing the causes of this disease mentioned previously. Smoking prevention and cessation are the chief methods of prevention. Radon can be removed from homes where it is present through proper ventilation. Asbestos exposure has been dramatically decreased recently by removing it from buildings and work environments.

BIOLOGIC CHARACTERISTICS AND MOLECULAR BIOLOGY

Cigarette smoke is a powerful mutagen that is strongly associated with the development of SCLC. Acquired hypermethylation of the promoter region of key genes is a common mechanism to inactivate tumor suppressor genes (TSGs) in tumor formation. The common molecular abnormalities in

TABLE 43-1 Molecular Anomalies Frequent in Small Cell Lung Cancer

Chromosomal Anomalies	Roles
Deletions or epigenetic inactivation of 3p, 5q, 13q, and 17p 3p21 (*RASSF1*, *FUS1*, *SEMA3B*, and *SEMA3* genes) 3p14.2 (*FHIT* gene) 3p24 (*RARβ* gene) 13q14 (*RB* gene) 17p13.1 (*p53* gene)	Disabled tumor suppressor genes
Amplifications of 1p, 2p, 3q, 5p, 8q, and 19p Telomerase *Bcl-2* genes Myc	Contain oncogenes promote survival and growth
Intracellular signal pathways Phosphoinositide 3-kinase/AKT/mTOR pathway P13K = mutated, overactive PTEN = mutated mTOR, S6K1, and 4EBT1 = active	Defective and lead to growth and survival
Receptor tyrosine kinases cKit and ligand (SCF) C-Met and ligand (HGF/SF) IGF-1R and ligand (IGF-1&2) FGFR 1-4 and ligand (FGF &2) VEGFR 1-3 and ligand (VEGF(A-E))	Overexpressed stimulating growth and survival
Molecular chaperones Heat shock protein (HSP)-90	Alters confirmation of client proteins Activates and inactivates proteins including AKT, MET, bcl-2, telomerase, survivin, and Apaf-1 Antiapoptotic
Cell surface proteins that are overexpressed NCAM (CD65) Gangliosides: FucGM1	Modulate growth, differentiation, and cell adhesion
Developmental pathways Hedgehog (Hh): Sonic hedgehog (SHh) Indian hedgehog (IHh) Desert hedgehog (DHh) Notch: Notch receptors 1-4 ligands: delta-1, Jagged 1 Jagged 2 WNT: multiple molecules SOX2	Cell proliferation Cell proliferation and neuroendocrine differentiation Leads to neuroendocrine differentiation Proliferative, differentiation, survival, and motility Proliferation of stem cells
Neuroendocrine marker proteins Synaptophysin Chromogranin A CD-56	
Histone modifying gene mutations Alters enzymes CREBBP, EP300, and MLL	

AKT, *V-akt murine thymoma viral oncogene;* Bcl-2, *B-cell lymphoma 2;* CD-56, *neural cell adhesion molecule;* cKit, *v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene;* C-Met, *met proto-oncogene;* CREBBP, *CREB binding protein;* EP300, *E1A binding protein p300;* FGFR1, *fibroblast growth factor receptor 1;* FHIT, *fragile histidine triad protein;* FucGM1, *ganglioside fucosyl-GM1;* FUS1, *cell FUSion1;* IGF-1R, *insulin-like growth factor 1 receptor;* MLL, *methyltransferase gene;* mTOR, *mammalian target of rapamycin;* Myc, *v-myc avian myelocytomatosis viral oncogene;* NCAM, *neural cell adhesion molecule;* P13K, *phosphoinositide 3-kinase;* P53, *tumor protein 53;* PTEN, *phosphatase and tensin;* RARβ, *retinoic acid receptor beta gene;* RASSF1, *ras association domain family member 1;* RB, *retinoblastoma;* SEMA, *sema domain;* SOX2, *SRY (sex determining region Y)-box 2;* VEGFR, *vascular endothelial growth factor receptor;* WNT, *wingless-type MMTV integration site family.*

SCLC are shown in Table 43-1.[6-8] A large number of genetic mutations are frequently observed in SCLC tumors, especially common in TSGs. The mutations lead to dysfunction of these suppressor molecules resulting in unrestricted tumor growth. It is common to find deletions or epigenetic inactivation of 3p, 5q, 13q, and 17p that contain a number of TSGs (Table 43-1). The chromosome 3 genetic deletions, observed in almost all cases, are found in both dysplastic and preneoplastic cells and have been demonstrated as the genetic mutations associated with the transformation of precancerous lesions into carcinoma. There has been substantial progress in understanding the molecular abnormalities leading normal bronchial epithelium to become carcinoma. However, there has not yet been much progress in preventing these events or reversing them once they have taken place.

Amplification or overexpression of 1p, 2p, 3q, 5p, 8q, and 19p are common. These contain oncogenes (Bcl-genes, myc and telomerase genes) that promote survival and growth of SCLC. Telomerase is unique in that it functions in the maintenance of telomeres, which are repeated nucleotide sequences at the ends of DNA molecules. Telomeres shrink over time leading eventually to cell death. The enzyme telomerase adds more nucleotides to the DNA ends and can confer immortality to tumor cells.

Intracellular signal pathways become defective leading to increased tumor growth and survival. These have been focus of much research in an attempt to develop effective targeted therapies. None of these are used in standard practice today. Molecular chaperones are large proteins that alter the conformation of client proteins leading to both activation and deactivation of pathways that can result in disregulation of normal cellular growth and development. Receptor tyrosine kinases are overexpressed stimulating growth and survival of SCLC through many pathways. Cell surface proteins are overexpressed modulating growth, differentiation, and cell adhesion.

Another biologic feature that distinguishes SCLC from NSCLC is the more frequent expression of neuroendocrine markers in SCLC. These neuroendocrine markers include enzymes (neuron-specific enolase and L-dopa decarboxylase), peptide hormones (gastrin-releasing peptide, arginine vasopressin), and surface markers such as neural cell adhesion molecule (NCAM). There are also peptide hormones that meet the criteria of autocrine growth factors, which require the production of a growth-promoting protein for which the producing cell has functional receptors. In the case of gastrin-releasing peptide, there is clear evidence that it is produced and secreted by many SCLC cells and then attaches to its cellular membrane receptors stimulating tumor growth.[9]

PATHOLOGY AND PATHWAYS OF SPREAD

The 2004 WHO classification defined SCLC as "a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli." The cells are round, oval, and spindle shaped. Nuclear molding is prominent. Necrosis is extensive, and the mitotic count is high. SCLC occurs in two variant forms: small cell carcinoma and combined small cell carcinoma. The latter type includes SCLC cells and any of the histologic types of NSCLC.[10]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, AND STAGING

The signs and symptoms of lung cancer depend on the location and bulk of the primary tumor, adenopathy, and metastatic disease. Because of the high frequency of extensive mediastinal and hilar nodal involvement in SCLC cases, patients frequently present with symptoms such as dyspnea, dysphagia, hoarseness, and superior vena cava (SVC) syndrome. Many patients with SCLC present with other thoracic symptoms including cough, hemoptysis, chest pain, and weight loss.

SCLC is the most common solid tumor associated with paraneoplastic syndromes. Several of these are endocrinologic or neurologic. The most common endocrinologic abnormality is the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). This condition results from the excessive secretion of ADH from tumor cells, leading to severe hyponatremia with resultant hypoosmolality. SIADH occurs in about 11% of patients with SCLC and typically resolves after response to anticancer therapy. Restriction of free water intake is critical to maintaining proper sodium concentrations before SIADH improves secondary to cancer therapy.[11] Atrial natriuretic peptides (ANP) or arginine vasopressin (AVP) syndromes also result in hyponatremia. Paraneoplastic syndromes associated with SCLC are found in Table 43-2.[12]

The neurologic syndromes associated with SCLC (Table 43-2) include Lambert-Eaton syndrome, cerebellar degeneration syndrome, encephalomyelitis, sensory neuropathy, and cancer-associated retinopathy. Each of these is observed in well under 5% of all patients with SCLC. Lambert-Eaton syndrome is an autoimmune disorder that affects calcium channels of the neuromuscular junction. Antibodies are directed against the calcium channels responsible for the presynaptic release of acetylcholine. These antibodies prevent the opening of calcium channels, which presents the release of acetylcholine. Patients with Lambert-Eaton syndrome present with myasthenia gravis–like symptoms of proximal myopathy, autonomic dysfunction, and hyporeflexia. Like many paraneoplastic syndromes, this condition is generally improved with response to anticancer therapy, although there can also be symptomatic responses to anti-myasthenia therapies.[13] The other neurologic syndromes are believed to be primarily autoimmune phenomena, which usually respond poorly to cancer therapy.[14,15]

SCLC can be diagnosed with histologic or cytologic sampling. In most cases, a diagnosis can be obtained via sputum expectoration, bronchoscopic sampling, or CT-guided transthoracic needle aspiration.

The VA Lung Cancer Study Group's Staging System, which distinguishes between limited and extensive SCLC, is most commonly used.[16] The initial definition of limited disease was an extent of intrathoracic disease encompassable within a "reasonable" radiation field. Investigators in recent years have recognized the dangers of variable interpretations and recent cooperative group trials require staging of patients with SCLC with the standard TNM system. However, the categorization of patients with SCLC into limited versus extensive stage disease has been extremely helpful for making rational treatment choices and designing trials.

Approximately two thirds of patients with SCLC have extensive-stage or stage IV disease at presentation. Staging evaluation would traditionally include a history and physical

TABLE 43-2 Paraneoplastic Syndromes Associated with Small Cell Lung Cancer

Syndrome	Manifestation(s)	Frequency (%)	Correctable with Therapy
SIADH	Hyponatremia	11	Yes
ANP or AVP syndrome	Hyponatremia	15	Yes
Ectopic ACTH or CRH production	Ectopic Cushing's syndrome	5	Rarely
Lambert-Eaton syndrome (antibodies to VGCC)	Myasthenia gravis–like symptoms	1-3	Yes
Other neurologic syndromes*	Other neurologic symptoms	<5	Rarely
Cancer-associated retinopathy	Visual loss	<1	Rarely

ACTH, *Adrenocorticotropic hormone;* ANP, *atrial natriureticpeptides;* AVP, *arginine vasopressin;* CRH, *corticotropin-releasing hormone;* SIADH, *syndrome of inappropriate antidiuretic hormone;* VGCC, *P/Q-type voltage gated calcium channels.*

**Other neurologic syndromes are often related to Hu antibody and include cerebellar degeneration, encephalopathy, sensory neuropathy, or opsoclonus/myoclonus.*

examination, complete blood cell count, chemistry panel, contrast-enhanced CT scan of the thorax and upper abdomen, pulmonary function testing, and CT or MRI scan of the brain. PET scans are quite accurate for the staging of this SCLC. PET scan can aid with the choice of appropriate therapy and radiotherapy (RT) planning by better identifying tumor extent.[17] PET/CT scanning can replace the traditional radiographic staging studies for SCLC with the exception of CT or MRI of the brain. Because of the high uptake of the tracer (radioactive glucose) within the normal brain, metastases are difficult to distinguish from the brain itself.

Investigators need to be cautioned regarding the influence of ever improving staging techniques on the interpretation of survival results. Many patients previously believed to have limited disease are currently "upstaged" to the extensive-disease category because of more sensitive staging studies. It is likely that their inclusion in the extensive-disease group and their exclusion from the limited disease category will improve survival rates of both groups. This effect is known as the *Will Rogers phenomenon*, which was first used in oncology regarding patients with SCLC and is based on Rogers's quote, "When the Okies left Oklahoma and moved to California, they raised the average IQ in both states." The best method of minimizing this potential bias is to perform properly stratified randomized trials.

There have been several efforts to identify prognostic factors other than staging as a means to better select patients for specific therapies. As with many malignancies, good performance status, young age, and female gender are associated with better prognosis, and these have been verified in large multivariate analyses.[18-21] The Mayo Clinic/North Central Cancer Treatment Group (NCCTG) evaluated 1598 patients with SCLC to determine prognostic factors. Multivariate analysis revealed that performance status, age, gender, number of metastatic sites, and baseline creatinine levels were all associated with survival of patients with E-SCLC. Among patients with L-SCLC, only age and gender were associated with survival.[20] One critical reason for determining prognostic factors is for use in the proper patient stratification and selection when designing trials.

One must consider a patient's pulmonary and cardiac fitness, ability to tolerate specific chemotherapeutic agents, prior malignancies, patient age, and performance status when making decisions regarding optimal therapy for patients with SCLC.

PRIMARY THERAPY LOCALLY ADVANCED DISEASE AND PALLIATION

Thoracic Radiotherapy in LSCLC

In the 1960s it was recognized that chemotherapy was quite active against SCLC and that patients treated with surgery or radiation alone did quite poorly. Therefore, chemotherapy became the primary therapy for SCLC.[22,23] Unfortunately, recurrence inevitably followed the response to chemotherapy and these relapses were most frequently in areas of previous disease. This pattern of failure led investigators to reexamine the use of TRT for L-SCLC. Today, both RT and chemotherapy have central roles in the treatment of SCLC.[24,25] A series of randomized trials were performed comparing chemotherapy alone to chemotherapy with TRT for patients with L-SCLC.[26-29] In 1992, two meta-analyses were published regarding the role of TRT in addition to chemotherapy.[2,29] Pignon et al reported a 3-year survival rate of 14.3% with combined-modality therapy compared to 8.9% with chemotherapy alone ($p = 0.001$). This 5.4% absolute difference in 3-year survival rates was identical to the 5.4% difference in 2-year survival ($p < 0.001$) in a similar meta-analysis reported by Warde and Payne. Although this 5.4% difference appears rather small, it represented a 61% increase in the 3-year survival of 8.9% achieved with chemotherapy alone.[29] In addition, the intrathoracic tumor control was improved by 25% with TRT.[2]

Sequencing and Timing of TRT and Chemotherapy

Chemotherapy and TRT can be delivered concurrently, sequentially, or in an alternating manner. Potential advantages of concurrent delivery include a shorter overall treatment time, increase in treatment intensity, and potential anticancer synergism between the various therapies. Disadvantages include the heightened toxicity and the inability to assess the antitumor response of the chemotherapy alone. The Japanese Clinical Oncology Group performed a Phase III trial in which patients with L-SCLC were randomized to sequential or concurrent therapy. All 231 patients received four cycles of EP every 3 weeks (sequential arm) or 4 weeks (concurrent arm) and were randomized to receive TRT during the first cycle of chemotherapy in the concurrent arm or after the fourth cycle in the sequential arm. TRT included 45 Gy (1.5 Gy twice daily) over 3 weeks. The median survival time was 19.7 months in the sequential arm compared with 27.2 months in the concurrent arm ($p = 0.097$). The 5-year survival rate for patients treated sequentially was 18.3% compared to 23.7% for those treated concurrently. Hematologic toxicity was more severe in the concurrent arm as was severe esophagitis which occurred in 9% in the concurrent arm and 4% in the sequential arm. The authors concluded that the findings strongly suggested that concurrent therapy was more effective for L-SCLC.[30] Although the p value was not significant, the trend favors concurrent therapy. The interpretation of this result is confounded by the difference in timing of TRT because TRT was initiated several months earlier in patients receiving concurrent therapy.

There have been conflicting results from the randomized trials that have addressed the issue of timing of TRT during chemotherapy. However, recent meta-analyses do help make sense of the contradictory data. One study analyzed randomized trials published after 1985 addressing the timing of TRT relative to chemotherapy in L-SCLC. Early TRT was initiated before 9 weeks after starting of chemotherapy and late TRT after 9 weeks. Seven trials ($n = 1524$ patients) met the inclusion criteria and were included. The relative risk of survival for early TRT compared to late TRT for all studies was 1.17 ($p = 0.03$), indicating an increased 2-year survival for patients undergoing early TRT. This translated to a 5.2% ($p = 0.03$) improvement in the 2-year survival for early TRT. This small but significant improvement in 2-year survival for early TRT was similar in magnitude to the benefit of adding TRT or PCI to chemotherapy.[31]

A subsequent meta-analysis investigated the influence of the time interval between the start of any treatment until the end of TRT (SER) on local tumor control, survival, and esophagitis. There was a significantly higher 5-year survival rate in the shorter SER arms (relative risk [RR] = 0.62; $p = 0.0003$), which was more than 20% when the SER was less than 30 days. A low SER was also associated with a higher incidence of severe esophagitis (RR = 0.55; $p < 0.0001$). Each week of extension of the SER beyond that of the study arm with the shortest SER resulted in an overall absolute decrease in the 5-year survival rate of 1.83%. Thus, earlier, shorter, more intense TRT programs improved survival.[32] The current Phase III trial, CALGB 30610/RTOG 0538, allows TRT to start with either the first or second cycle of chemotherapy. Given the complexity of modern RT planning and the urgency to initiate therapy in patients with SCLC, the majority of patients treated in the United States and Europe appear to receive TRT starting with the second cycle of chemotherapy.

Thoracic Radiation Therapy Dose

SCLC is considered a radioresponsive malignancy because the low doses of TRT previously used produced encouraging responses. Total TRT doses for L-SCLC have ranged from 25 Gy to 30 Gy in 10 fractions in the 1970s to up to 70 Gy in 35 fractions in recent years. Doses in the lower end of this range may have been acceptable when chemotherapy was less effective and disseminated disease occurred earlier in the disease course. Improvements in systemic therapy have increased the need for aggressive TRT regimens that produce more durable responses. It was estimated by Choi and Carey that the risk of intrathoracic tumor failure at total doses of 40 Gy or less was 80%,[33] which was confirmed in a National Cancer Institute of Canada (NCIC) L-SCLC trial in which patients were randomized between 25 Gy over 10 fractions versus 37.5 Gy over 15 fractions.[34] The 2-year actuarial rates of local failure were 80% and 69%, respectively.

The most commonly administered doses of TRT range from 45 Gy to 70 Gy in 1.8 Gy to 2.0 Gy daily fractions. Most trials estimated the local control rates in this dose range between 58% and 85%.[35] Cancer and Leukemia Group B (CALGB) investigators have explored high-dose conventionally fractionated TRT in detail. A Phase I trial suggested 70 Gy was feasible given with the fourth cycle of chemotherapy with provocative 5-year survival of 36%, albeit in a select cohort of patients.[36] Subsequent Phase II trials, where TRT was given with the third cycle of (carboplatin based) chemotherapy have reported mixed results. Pooled data from these prospective studies include 200 patients assigned to receive TRT of 70 Gy (35 daily fractions of 2.0 Gy) with median follow-up of 78 months. Treatment was relatively well tolerated (grade 3 or greater esophagitis was 23%), and median survival was similar to reports with 45 Gy (1.5 Gy twice daily). The median survival for the entire cohort assigned to 70 Gy TRT was 19.9 months and 5-year survival rate was 20%. This experience may aid practitioners decide whether high-dosage daily RT with platinum-based chemotherapy is appropriate outside of a clinical trial.[37,38]

The feasibility of high-dose daily TRT coupled with the fact that the majority of patients are treated with daily TRT in clinical practice has resulted in a Phase III trial (CALGB 30610/RTOG 0538) comparing EP and concurrent TRT with either 45 Gy in 30 twice-daily fractions or 70 Gy in 35 daily fractions.[37] A Phase III trial conducted in Europe has also directly addressed the question of high-dose once-daily TRT. The CONVERT Trial randomized more than 500 patients to receive 66 Gy in 2 Gy daily fractions or 45 Gy in 1.5 Gy twice-daily fractions starting with the second cycle of chemotherapy. The trial recently completed accrual and results should be reported in the next few years.[39]

TRT and Altered Fractionation

In addition to increasing the number of daily treatments, another means of intensifying TRT is the use of altered radiation fractionation. For patients with L-SCLC, most altered fractionation strategies have employed twice-daily fractionation with fraction sizes varying from 1.1 Gy to 1.8 Gy and total doses ranging from 40 Gy to 54 Gy. Most regimens have tested the principle of accelerated hyperfractionation in which a twice-daily regimen allows the delivery of a standard total TRT dose over a shortened duration. These regimens should provide an improved therapeutic index for patients with rapidly growing tumors such as SCLC with a small shoulder and a steep slope on their in vitro cell survival curves.

Several encouraging pilot studies led to the development of Intergroup Trial 0096, a Phase III trial testing the concept that accelerated hyperfractionation would improve the outcome for patients with L-SCLC (Table 43-3). The experimental regimen was 45.0 Gy in 1.5 Gy twice-daily fractions beginning on day 1 of a four-cycle regimen of EP. The interfraction interval was 6 to 8 hours and the elapsed treatment time was 19 to 21 days. A total of 419 patients were randomized between the TRT regimens of 45.0 Gy in 1.8 Gy daily fractions compared to 45.0 Gy in 30 to 1.5 Gy twice-daily fractions. Of these, 10 treatments were often given with off cord oblique fields (afternoon session of the final 2 weeks) and dose to the spinal cord was limited to 36 Gy. In both arms the TRT began on day 1 of a four-cycle course of EP. There was a significant survival advantage for the patients with twice-daily TRT s compared to the patients with daily TRT with 5-year survival rates of 26% and 16%, respectively ($p = 0.04$). The median survival time was 19 months for the daily TRT group and 23 months for the twice-daily TRT. The intrathoracic tumor failure rate was 36% for the twice-daily TRT arm and 52% for the daily TRT arm ($p = 0.06$). The principal difference in toxicity was a higher rate of grade 3 esophagitis in the twice-daily TRT arm: 27% versus 11% ($p < 0.001$).[40] This study confirms the principle that an intensification of TRT beyond the relatively low dose daily TRT can improve both local control and survival. This trial has altered the standard of care of patients with L-SCLC because this twice-daily fractionation program is considered to be the standard by which all other programs are compared.

TABLE 43-3 Intergroup 0096 Study Comparing Once- with Twice-Daily Thoracic RT for Patients with L-SCLC Treated with Concurrent Cisplatin and Etoposide

Characteristic	Arm 1 (Once Daily)	Arm 2 (Twice Daily)	*p* Value
Number of patients	206	211	—
Median survival time (mo)	19	23	—
2-year survival rate	41%	47%	—
5-year survival rate	16%	26%	0.04
Failure-free survival rate	24%	29%	0.10
Local failure rate	52%	36%	0.06
Simultaneous local and distant failure rate	23%	6%	0.005
Grade 3 esophagitis rate	11%	27%	<0.001

L-SCLC, *Limited-stage small cell lung cancer;* RT, *radiation therapy.*

The North Central Cancer Treatment Group (NCCTG) performed a trial (89-20-52) that has been misinterpreted as contradicting the findings of the Intergroup Trial 0096. This trial included 310 patients with L-SCLC initially treated with three cycles of EP.[41] Subsequently, the 261 patients without progression were randomized to two cycles of EP plus either daily TRT (50.4 Gy in 28 fractions) or split-course twice-daily TRT (24 Gy in 16 fractions, 2.5 week break and 24 Gy in 16 fractions). Patients then received a sixth cycle of EP followed by PCI. The median and 5-year survival rates were 20.6 months and 21% with daily TRT compared with 20.6 months and 22% for twice-daily TRT($p = 0.68$). The findings of these two Phase III studies comparing daily to twice-daily TRT for L-SCLC led to the conclusion that continuous course of twice-daily TRT is better than daily TRT, but split course twice-daily RT is not.

There has also been investigation of higher doses of twice-daily RT in an attempt to further improve outcome. NCCTG

95-20-53 was a Phase II trial that included six cycles of EP.[42] PCI (25 Gy over 10 fractions) was delivered during cycle three. Cycles four and five included concurrent EP and TRT (30 Gy over 20 twice-daily fractions, a 2-week break, and 30 Gy over 20 twice-daily fractions). The 5-year survival rate of the 76 evaluable patients was 24% (median, 20 months). The 5-year survival rate of the 64 patients who received TRT was 29% (median, 22 months). The 5-year cumulative incidence of in-field failure was 34%. This high-dose twice-daily TRT regimen resulted in a favorable 5-year survival rate. Local failure remains a problem that will require further investigation. Newer technology should allow the safe administration of greater doses of TRT that should improve outcome. Schild et al evaluated data from this trial and others to demonstrate a positive correlation between biologically effective dose (BED) and 5-year survival.[42]

A hybrid approach of concomitant boost TRT has been investigated by the RTOG in both a Phase I and a Phase II setting.[43,44] A dose of 61.2 Gy was given with the first cycle of EP in the Phase II study with twice-daily TRT given during the final 9 days of therapy. Although encouraging local tumor control was reported, overall survival was less than predicted. This regimen was initially included as one of the experimental treatment arms on the CALGB 30160/RTOG 0538 trial, though the concomitant boost arm was discontinued after a planned interim analysis of toxicity between the two experimental arms. As noted previously, the CALGB 30160/RTOG 0538 trial continues as a direct comparison of 45 Gy twice-daily TRT with 70 Gy daily TRT, testing the hypothesis that the higher BED twice-daily regimen will improve survival.

Chemotherapy

The selection of chemotherapeutic agents to combine with TRT for patients with L-SCLC is largely based on trials of multiagent regimens used for E-SCLC. The currently accepted standard chemotherapy regimen for both E-SCLC and L-SCLC in the United States is the two-drug regimen of EP. SWOG was the first group to report a completed trial of concurrent TRT with EP for L-SCLC. They reported a median survival time of 17.5 months and 4-year survival rate of 30%, which appeared superior to the previously reported results with TRT combined with other non–platinum-containing regimens.[45] Additionally, promising results were subsequently reported with TRT and EP and were confirmed in the Intergroup Trial 0096.[46-48] No randomized trial has demonstrated the superiority of TRT and EP over any other regimen for L-SCLC.

New Agents

A recent Japanese Trial compared irinotecan and cisplatin compared with EP for E-SCLC. The median survival was 12.8 months with irinotecan and cisplatin compared to 9.4 months with EP ($p = 0.002$).[48] A similarly designed SWOG Trial S0124 was unable to confirm a survival advantage obtained by irinotecan and cisplatin.[49] Hanna et al reported similarly negative findings from a third similar Phase III trial.[50] Paclitaxel has also been studied extensively in SCLC. A Phase III study in extensive stage disease showed increased fatal toxicity without an improvement in survival with the addition of paclitaxel to EP.[51] A Phase II RTOG trial in LSCLC demonstrated that paclitaxel could be given together with EP during twice-daily TRT, though overall survival did not appear to be better than prior studies using only two chemotherapy drugs.[52] In this age of targeted biological therapy, many compounds have been tested, with a particular interest in antiangiogenic agents, including bevacizumab, in extensive stage disease. These agents have generally demonstrated improved progression-free survival but not overall survival, though results of a completed Phase III trial assessing bevacizumab in extensive disease[53] are pending. The integration of targeted agents in L-SCLC should be undertaken with caution and not done outside of a clinical trial, given that severe tracheoesophageal fistula has been reported in pilot studies using bevacizumab with TRT.[54]

Role of Surgery

The use of resection as primary management of SCLC was largely abandoned by the 1970s when poor survival rates were reported and few complete resections were achieved.[55] In a report by the VA Surgical Oncology Group published in 1982, 5-year survival rates for patients with resected T1N0, T1N1, and T2N0 SCLC were 60%, 31%, and 28%, respectively.[56] All of these patients received chemotherapy. A SWOG protocol enrolled 15 patients with L-SCLC who underwent resection followed by chemoradiation and found this group to have a better 2-year survival rate than a cohort of matched patients treated nonoperatively in other SWOG trials (45% versus 14%).[57] Ichinose et al reported on 112 patients with SCLC who underwent surgical resection and were then randomized between two chemotherapy regimens.[58] Although the chemotherapy regimens produced comparable outcomes, the 3-year survival rates were encouraging: 65% for N0 disease, 52% for N1 disease, and 29% for N2 disease. Chandra et al also found a favorable 5-year survival of 38% in patients with stages I and II SCLC who had resections performed.[59] Each of these three reports suggests that for patients with the rare N0 or N1 L-SCLC, resection followed by chemotherapy produced survival results that may be superior to nonoperative approaches. The role of TRT in this setting remains unclear. A pattern-of-failure study of patients with resected SCLC receiving postoperative chemotherapy alone would help clarify this issue.

A randomized trial was conducted by the Lung Cancer Study Group in which patients with L-SCLC achieving a partial response (PR) or complete response (CR) to chemotherapy received either resection or none.[60] There was no survival difference between the arms, with a 2-year survival rate of 20% in both arms ($p = 0.55$). Based on this trial and on the proven survival benefit of concurrent chemotherapy and TRT, adjuvant surgery following chemotherapy is not recommended.

There are limited data regarding the role of resection of intrathoracic recurrences. Shepherd et al reported on 28 patients with L-SCLC who underwent salvage surgery following either a PR to chemotherapy or subsequent progressive disease.[61] Ten of these 28 patients had NSCLC elements in their specimen. Their 5-year survival rate was 23%. There are only anecdotal data regarding surgical salvage of patients initially treated with both chemotherapy and TRT. Although there may be a role for resection in patients with stages I or II SCLC, it is unclear that surgical intervention would provide a benefit when compared to TRT for similar volumes or stages of disease. While it appears that some patients may be salvaged after a PR or local failure, resection has not been widely employed. This may be as a result in part of the propensity of SCLC to metastasize.

Prophylactic Cranial Irradiation for Both L-SCLC and E-SCLC

PCI was initially introduced into practice in the 1960s for patients with acute lymphoblastic leukemia who had a high risk of failure in the central nervous system (CNS).[62] It was first tested for patients with SCLC in the 1970s following the recognition that brain metastases were frequent. The blood-brain barrier prevents the penetration of most chemotherapeutic agents leaving the brain as a sanctuary site for relapse.

PCI has been shown to improve survival of patients who achieve a CR. Auperin et al published a meta-analysis that included data from seven Phase III studies that compared PCI to no PCI after a CR was achieved.[63] As in the TRT meta-analyses, the 3-year survival rate was 5.4% better for those who received PCI at 20.7% compared with 15.3% for those with no PCI ($p = 0.01$). Although 5.4% appears small, it does reflect a 35% increase in 3-year survivors.

PCI is important for the majority patients with E-SCLC. Slotman et al conducted a randomized trial (EORTC 08993-22993) of PCI in patients with E-SCLC who had had any degree of response to chemotherapy.[64] Patients received either PCI or no further therapy (control group). The PCI included 20 Gy in 5 to 8 fractions, 24 Gy over 12 fractions, 25 Gy in 10 fractions, or 30 Gy over 10 or 12 fractions. The cumulative risk of brain metastases within 1 year was 14.6% in the PCI group and 40.4% in the control group (hazard ratio, 0.27; $p < 0.001$). PCI was associated with an increase in median survival from 5.4 months to 6.7 months. The 1-year survival rate was 27.1% in the PCI group and 13.3% in the control group ($p = 0.003$). PCI had side effects but did not have a significant effect on global health status. The largest mean difference between the two arms was observed for fatigue and hair loss, which were greater with PCI.[65] PCI reduced brain metastases and prolonged survival.[64] PCI should be standard care for all patients with SCLC who have any degree of favorable response to initial chemotherapy. This trial did not evaluate which dose-fractionation regimen was best.

The optimal PCI regimen would include the following desirable characteristics: decreases brain metastases, increases survival, takes the least time from the patients' remaining life, decreases cost, and causes the least toxicity. An international consortium studied dose-fractionation in a Phase III trial. Le Pechoux reported the results of this study that compared standard to higher doses of PCI. This trial included 720 patients with L-SCLC in CR after chemotherapy and TRT. Patients were assigned to either standard ($n = 360$, 25 Gy over 10 fractions) or high-dose PCI ($n = 360$, 36 Gy). The high-dose PCI was either conventional (18 daily fractions of 2 Gy) or accelerated hyperfractionated (24 twice-daily fractions of 1.5 Gy) regimens. There was no significant difference in the 2-year incidence of brain metastases between the standard PCI group and the higher-dose group at 29% and 23%, respectively ($p = 0.18$). The 2-year overall survival was 42% in the standard-dose group and 37% in the higher-dose group ($p = 0.05$). The most common acute toxic events were fatigue, 30% in the standard-dose group compared to 34% in the higher-dose group, headache 24% compared to 28%, and nausea or vomiting 23compared to 28%. They concluded that although there was not a significant decrease in brain metastases after higher-dose PCI, there was a significant increase in mortality. Therefore, they concluded that PCI at 25 Gy over 10 fractions should be the standard of care for SCLC.[66] Although this trial did not address the effects of dose-fractionation for patients with E-SCLC, it is still the most compelling data available regarding the regimen used for PCI for patients with SCLC. While the 25 Gy in a 10-fraction regimen did not meet all the characteristics for the optimal regimen, it was associated with better survival, decreased patient time required, and decreased healthcare costs.[66]

Based on the currently available data, it is recommended that patients with SCLC achieving any degree of response to initial therapy should be offered PCI.[67] The current standard dose-fractionation pattern is 25 Gy over 10 fractions.[67,68] There are also data from a pooled retrospective NCCTG analysis that found that PCI benefits patients who have stable disease after initial therapy. Thus, it appears likely this group of patients benefits from PCI as do those with a favorable response.[67]

MANAGEMENT OF METASTATIC AND RECURRENT DISEASE

Approximately two thirds of all patients with SCLC have extensive-stage disease.[2] The most common sites of extrathoracic metastases are the liver, bone, brain, and adrenal glands.

Initial management of most patients with newly diagnosed ESCLC is four or more cycles of EP. Novel targeted agents are the focus of much research and it is hoped that newer agents will improve outcomes. Second-line chemotherapy often includes topotecan because this was proven superior to best supportive care in patients failing initial therapy.[69]

The Role of Non-CNS Radiotherapy for E-SCLC

RT also has important use for E-SCLC. One role for RT is to palliate bulky intrathoracic disease causing airway compromise, cough, hemoptysis, postobstructive pneumonia, or SVC syndrome. This is often accomplished with a short regimen such as 30 Gy over 10 fractions (or shorter), which will improve symptoms in the majority of patients.

Although the role of TRT is less clear in patients with E-SCLC, there appears a distinct survival benefit to delivering TRT to carefully selected patients. Jeremic et al performed a Phase III study that evaluated chemotherapy with or without TRT in patients with E-SCLC. Patients initially received three cycles of carboplatin and etoposide. Those patients with a CR at distant sites and a PR or better in the chest were randomly assigned to receive either twice-daily TRT (54 Gy in 36 fractions) plus concurrent carboplatin and etoposide followed by two cycles of the same chemotherapy or four cycles of the same chemotherapy without TRT. All patients with a CR at the distant sites also received PCI. Patients who received TRT had significantly better survival than those who did not (median survival time, 17 versus 11 months; 5-year survival rate, 9.1% versus 3.7%; $p = 0.041$).[70] This study revealed improved survival from TRT in carefully selected patients with E-SCLC. It appears that patients who benefit are those for whom the RT encompassed all known residual disease within the body.

The hypothesis that RT can be added to chemotherapy to more effectively treat E-SCLC was evaluated further in a Mayo Clinic Trial. Bonner et al performed a trial that explored the use of RT for both the thoracic and metastatic lesions. This study included an aggressive regimen of seven cycles of an alternating six-drug combination. The first cycle consisted of cyclophosphamide, doxorubicin, etoposide, vincristine, and lomustine. Subsequent cycles used a regimen of doxorubicin alternating with cisplatin.[71] PCI and TRT were given during the chemotherapy. PCI was delivered during the first week of chemotherapy cycles two and three (17 Gy in 5 fractions, each of 3.4 Gy, during each week for a total of 34 Gy in 10 fractions). The TRT was delivered in a split-course fashion during the first week of chemotherapy cycles five and six (20 Gy over 5 fractions, each of 4 Gy, during each week for a total of 40 Gy in 10 fractions). After the seven cycles, patients received 6 Gy in 1 fraction upper hemibody RT followed by 8 Gy in 1 fraction lower hemibody RT. Thirteen patients completed the initial seven cycles. Two of the 20 (10%) patients had fatal hematologic complications after lower hemibody RT. Three (15%) patients had severe peripheral neurologic toxicity, two (10%) had severe central nervous system toxicity, and one (5%) had severe cardiac toxicity. The median survival time was 11.5 months and 5-year survival rate was 16%.

There are valuable lessons to be learned from these data. First, this therapy was toxic. The collective hematologic toxicity from six drugs combined with the TRT, PCI, and sequential

upper and lower hemibody RT resulted in 10% (2 of 20 patients) mortality. Irradiating the entire marrow led to excessive marrow suppression, toxicity, and mortality. Additionally, the PCI regimen (34 Gy in 10 fractions) given during chemotherapy was associated with an unacceptably high risk of leukoencephalopathy.[72] It appears best to administer the PCI after all other therapy because concurrent chemotherapy plus PCI further increases the risk of leukoencephalopathy. Despite the toxicity issues, the finding that the 5-year survival of 16% was much better than other trials for patients with E-SCLC. It is quite possible that RT to the sites of initial disease or areas of residual disease that persist after chemotherapy could be helpful, because failures following chemotherapy alone frequently occur in the sites of original disease and RT lowers the risk of such recurrences. This is the basis of a currently opened RTOG trial 0937, a Phase II trial for patients with E-SCLC and four or fewer distant metastases. This randomized trial compares chemotherapy followed by either PCI (standard arm) or PCI plus TRT and involved field RT to all sites of remaining disease after chemotherapy. The primary endpoint is survival.

The Treatment of Metastases

Patients with brain metastases at diagnosis require cranial RT in their initial management, usually concurrently with the first or second cycle of chemotherapy. The whole-brain RT doses most commonly used for brain metastases range from 20 Gy in 5 fractions to 37.5 Gy in 15 fractions. The majority of patients receive effective palliation as a result.

Patients with a few or solitary primary or recurrent brain metastases can be considered for more aggressive treatment options such as radiosurgery. There is little data addressing specialized therapy such as radiosurgery for patients with SCLC. Sheehan performed a retrospective review of 27 patients with 47 recurrent SCLC brain metastases who underwent radiosurgery.[73] The overall median survival was 18 months after the diagnosis of brain metastases. They concluded that radiosurgery for recurrent SCLC metastases provided effective local tumor control in the majority of patients.

One particular subgroup of patients with E-SCLC included those with disease limited to the chest and the brain only. This group may benefit from the use of chemotherapy, whole-brain RT, and TRT. Kochhar et al identified 30 such patients who initially received cisplatin-based chemotherapy and concomitant whole-brain RT consisting of 36 Gy to 48 Gy.[74] Subsequently, 22 patients also received TRT. The median survival was 14 months. The outcome of patients with E-SCLC with the brain as the sole site of metastases at diagnosis was similar to patients with L-SCLC. Of this cohort, patients who received TRT tended to have a longer median survival (16 months) than those who did not receive TRT or who received it at the time of local disease progression (12 months; $p = 0.3$). This concept of treating E-SCLC with chemotherapy and irradiating all known gross disease probably explains the favorable results in the study of Kochhar et al and the extraordinary 5-year survival rate of 16% achieved in the Mayo Trial reported by Bonner et al.[71] Currently, the RTOG is performing RTOG 0937, previously described, to more fully evaluate the role of RT for carefully selected patients with E-SCLC.

Sites of metastatic involvement may also require palliative RT for effective symptom management. These include painful or weight-bearing bony lesions, symptomatic adrenal metastases, or soft-tissue masses. Lesions causing any debilitating symptoms can be considered for palliative RT.

SVC syndrome may also develop in patients with SCLC. This appears more frequent with this histology than others as a result of a propensity to develop bulky mediastinal adenopathy. Chan et al reported on 76 consecutive patients with SCLC with SVC syndrome,[75] and 93% had improvement in SVC symptoms after chemotherapy compared with 94% after TRT. Additionally, a favorable response was obtained with a wide range of RT fractionation patterns and total doses administered. Those who received chemotherapy and TRT had a longer time to recurrence of SVC syndrome ($p = 0.018$) compared to those who received chemotherapy alone. The early mortality from SVC syndrome was 2%. Chemotherapy or TRT was effective initial treatment in patients with SCLC with SVC syndrome. They also concluded that there is no need to use large radiation fraction sizes for the first few treatments. TRT resulted in more durable palliation than achieved with chemotherapy alone. This study debunked the myth that RT needs to begin emergently within hours. It is preferable to begin chemotherapy quickly and take adequate time for optimal RT treatment planning. This will decrease the normal tissue volumes within the fields and insure that the entire tumor is irradiated.

Management of Recurrent SCLC

The prognosis of any patient with recurrent SCLC is grave, regardless of the site of relapse. Although there are responses noted to second-line chemotherapy, these responses are usually short-lived and often precede rapid tumor progression. Palliative or salvage RT or re-RT (including reirradiating brain metastases) can be of substantial benefit to such patients.

TECHNIQUES OF IRRADIATION

Treatment is dependent on accurate identification of the disease and a clear understanding of its exact distribution with relationship to normal structures. The combination of PET scans and CT imaging are helpful in defining the extent of disease except within the brain. Within the chest, functional imaging (PET) allows better detection of viable tumor within a structure and the CT is better to define the exact extent and location of these structures. Incorporating both PET and CT scans into RT planning can be used to generate smaller, more precise tumor fields that may further decrease toxicity while treating all gross disease with RT. Over time, improvements in imaging allow physicians to more precisely locate and irradiate all sites of disease.

Treatment Volumes and Normal Tissue Considerations

The ability of a patient with L-SCLC to tolerate increasingly aggressive RT regimens and higher total doses during concurrent chemotherapy is in part related to improved TRT target volume selection.[35] There emerged evidence in the 1980s and 1990s that the use of smaller radiation fields did not adversely influence tumor control in patients receiving concurrent cisplatin-based chemotherapy. The fields employed in Intergroup Trial 0096 confined the high-dose volume to the tumor with a 1.5-cm margin, the ipsilateral hilum, and the mediastinum from the thoracic inlet to the subcarinal region. The contralateral hilum and supraclavicular regions were excluded. These treatment volumes have been widely adopted in subsequent clinical trials.

Smaller volumes have the advantage of further sparing of the surrounding normal tissues: lung, esophagus, heart, spinal cord, and bone marrow (Figure 43-1). Optimal sparing is important to decrease the high risk of severe morbidity from therapy. We compiled the toxicity experienced by patients treated on NCCTG 89-20-52, which included concurrent chemotherapy plus either daily or twice-daily TRT. The most common toxicity was hematologic; 90% of patients had grade

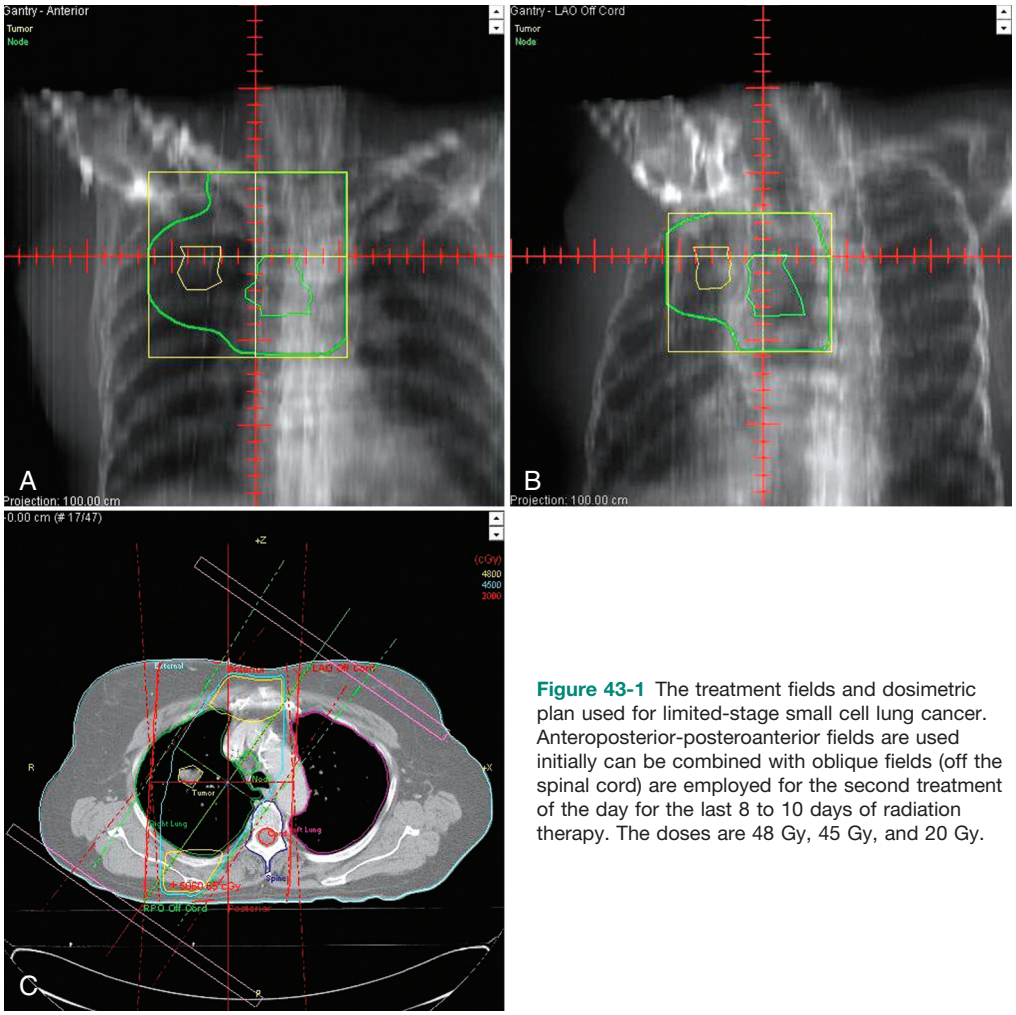

Figure 43-1 The treatment fields and dosimetric plan used for limited-stage small cell lung cancer. Anteroposterior-posteroanterior fields are used initially can be combined with oblique fields (off the spinal cord) are employed for the second treatment of the day for the last 8 to 10 days of radiation therapy. The doses are 48 Gy, 45 Gy, and 20 Gy.

3 or greater (3+) hematologic toxicity and 43% had grade 4+ hematologic toxicity. Forty-seven percent of patients had grade 3+ nonhematologic toxicity and 11% had grade 4+ nonhematologic toxicity. Nausea, vomiting, and esophagitis were the most common nonhematologic toxicities. Fatal toxicity occurred in four patients (2%) of patients.[41] Thus, smaller, more precise fields are needed to deliver therapy more safely. Prospective trials in Europe have evaluated an approach of "involved field" radiotherapy in LSCLC. An initial trial using CT directed radiotherapy fields reported an 11% isolated nodal relapse, whereas isolated nodal relapse was only 3% in a follow-up study that included both CT– and FDG-PET–based disease.[76-78] The current Phase III trial, CALGB 30610, does not employ elective mediastinal radiotherapy, though level 1 evidence regarding elective nodal irradiation is lacking.

RT-induced toxicity is related to dose-volume parameters. In a classic study, Graham et al reported that the risk of grade 2+ pneumonitis was 0% when the V20 (total lung volume that received ≥20 Gy) was <22%, 7% when the V20 was 22% to 31%, 13% when the V20 was 32% to 40%, and 36% when V20 was >40%.[79] The ongoing Phase III study (CALGB 30610) recommends limiting the V20 lung to <40%, although this can be difficult to achieve when bulky disease is present. It is generally accepted that the spinal cord can safely receive 45 Gy to 50 Gy in 1.8 Gy to 2.0 Gy fractions. In most twice-daily TRT regimens employing 1.5 Gy fractions, the spinal cord is limited to 36 Gy to 37 Gy without incident.[41] In the Intergroup 0096 regimen, the oblique off cord fields were used for the second daily treatment for the last 8 to 10 treatments. The TD5/5 (toxic dose to 5% of patients in 5 years) was estimated at 60 Gy for one third of the heart, 45 Gy for two-thirds of the heart, and 40 Gy for the entire heart.[80] Esophagitis is related to the dose of radiation, volume of esophagus irradiated the fractionation schema, and the timing of chemotherapy. Of the patients in the Intergroup Trial 0096 who received twice-daily TRT, 32% had grade 3+ esophagitis compared with 16% for those who received twice-daily TRT ($p = 0.001$).[40] Although esophagitis is uncomfortable, can lead to dehydration, and the need for intravenous hydration or hospitalization, this should not be used as reasons to deny fit patients twice-daily TRT.

Watkins described the factors associated with development of severe acute esophagitis during twice-daily TRT with concurrent chemotherapy in patients with L-SCLC. Twice-daily chemoradiotherapy included 45 Gy at 1.5 Gy twice daily with concurrent platinum-based chemotherapy. The most strongly associated dosimetric variable was the V15 (grade 3 esophagitis rates of 15% versus 64% for V15 <60% versus >60%, respectively).

TREATMENT ALGORITHM, CONTROVERSIES, PROBLEMS, CHALLENGES, FUTURE POSSIBILITIES, AND CLINICAL TRIALS

A proposed treatment algorithm for patients with SCLC is shown in Figure 43-2.

L-SCLC with Good Performance Status and TRT

The management of SCLC is dependent on stage and medical fitness. For patients with good performance status and L-SCLC, the recommended therapy would include concurrent TRT with EP chemotherapy. Specifically, the treatment with the best evidence justifying its use is four cycles of EP chemotherapy with twice-daily TRT beginning early.[31,32] The twice-daily TRT is delivered in 1.5 Gy fractions with an interfraction interval of more than 6 hours to a total dose of 45.0 Gy. This recommendation is based on the Intergroup Trial 0096.[40] The Cancer and Leukemia Group B/Radiation Therapy Oncology Group trial (CALGB 30610/RTOG 0538) and CONVERT trial will help determine which of two TRT regimens is best.

For patients with huge tumors, postobstructive pneumonia, or atelectasis, there may be value in delaying initiation of TRT until a later cycle of chemotherapy. This may be necessary in some cases if the initial tumor volume would require an excessive volume of normal lung to be irradiated. It is unknown if adding TRT improves the outcome of the rare patient with resected L-SCLC. However, chemotherapy is generally administered after resection.

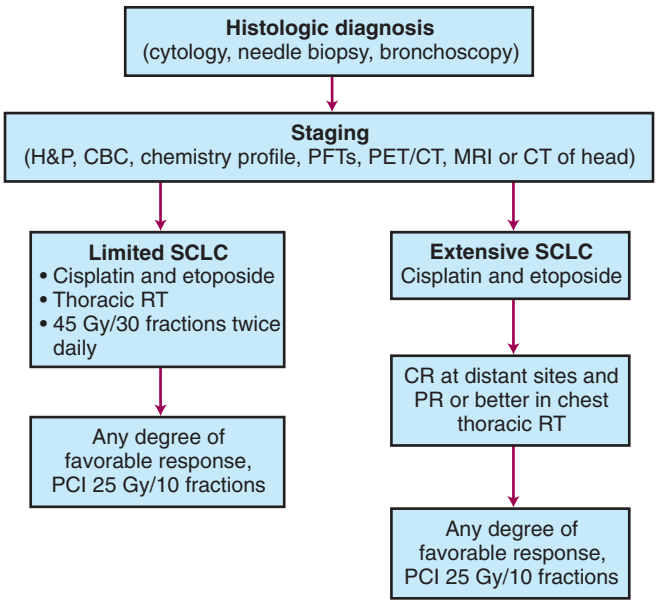

Figure 43-2 Treatment algorithm for small cell lung cancer. *CBC,* Complete blood counts; *CR,* complete response; *CT,* computed tomography; *MRI,* magnetic resonance imaging; *PCI,* prophylactic cranial irradiation; *PET,* positron emission tomography; *PFT,* pulmonary function test; *PR,* partial response; *RT,* radiotherapy; *SCLC,* small cell lung cancer.

L-SCLC in Special Populations: The Elderly and Those with a Lower Performance Status

Treatment in fit elderly patients (>70 years of age) can be carried out in a manner similar to fit younger individuals. NCCTG 89-20-52 included 263 patients with L-SCLC and an ECOG performance status of <2 who were randomized to daily TRT or split course twice-daily TRT. The outcomes of the younger patients (<70 years old) were compared to the elderly patients (>70 years old). The overall incidence of grade >3 (3+) or grade >4 (4+) toxicity was not significantly greater in elderly patients. One specific toxicity, grade 4+ pneumonitis occurred in 0% of those <70 years compared to 6% of older patients ($p = 0.008$). Grade 5 toxicity occurred in 3 of 54 (5.6%) patients >70 years old compared with 1 of 209 (0.5%) younger individuals ($p = 0.03$). Overall survival was not significantly worse in older individuals; the 5-year survival rates were 22% in younger patients compared with 17% in older patients ($p = 0.14$). Fit elderly patients with L-SCLC can receive combined-modality therapy, if carefully monitored, with a reasonable expectation of 5-year survival.[81]

Patients with lower performance status tolerate the aggressive twice-daily TRT and EP more poorly. However, there is still a likely benefit to concurrent chemoradiation for these patients, particularly if their reduced functional status is as a result of tumor. One alternative would be to deliver daily TRT in 1.8 Gy 2.0 Gy fractions to 50 Gy to 70 Gy, while sparing the spinal cord above 45 Gy to 50 Gy. This could be delivered beginning with the first or second cycle of chemotherapy. Judgment and flexibility are critical when treating very old (≥80 years) or patients who are have poor performance status. It is also reasonable to administer sequential therapy to patients who can not tolerate the rigors of concurrent therapy.

E-SCLC and TRT

Initial management of E-SCLC involves primary chemotherapy (EP), with RT being reserved for brain metastases, bulky and symptomatic intrathoracic disease, and symptomatic bony or visceral metastatic sites. In addition, patients with a good performance status, a CR of metastatic disease, and at least stable disease in the chest following chemotherapy may benefit from the addition of TRT.[70]

Prophylactic Cranial Irradiation for Both E-SCLC and L-SCLC

PCI should be considered for all patients with SCLC who have achieved any degree of favorable response following initial management with chemotherapy or chemoradiation; 25 Gy in 10 fractions is considered the most standard regimen.[66]

Controversies and Clinical Trials

Issues addressed in current clinical trials include the potential benefits of higher dose daily TRT regimens in the management of L-SCLC. In E-SCLC, most research focuses on systemic therapy. However, there is a trial open examining whether patients benefit from the administration of RT to the chest and sites of residual disease plus PCI compared to PCI alone following systemic chemotherapy.

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