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Daniel Almquist
UNMC

Kailash Mosalpuria
UNMC

Apar Kishor Ganti
UNMC, aganti@unmc.edu

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Almquist, Daniel; Mosalpuria, Kailash; and Ganti, Apar Kishor, "Multimodality Therapy for Limited-Stage Small-Cell Lung Cancer" (2016). *U.S. Department of Veterans Affairs Staff Publications*. 104.
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Multimodality Therapy for Limited-Stage Small-Cell Lung Cancer

Daniel Almquist, MD, Kailash Mosalpuria, MD, MPH, and Apar Kishor Ganti, MD, MS

University of Nebraska Medical Center; and Veterans Administration Nebraska–Western Iowa Health Care System, Omaha, NE

Abstract

Limited-stage small-cell lung cancer (SCLC) occurs in only one third of patients with SCLC, but it is potentially curable. Combined-modality therapy (chemotherapy and radiotherapy) has long been the mainstay of therapy for this condition, but more recent data suggest a role for surgery in early-stage disease. Prophylactic cranial irradiation seems to improve outcomes in patients who have responded to initial therapy. This review addresses the practical aspects of staging and treatment of patients with limited-stage SCLC.

INTRODUCTION

In the United States, the proportion of small-cell lung cancers (SCLCs) has decreased from approximately 25% of all lung cancers in 1993 to approximately 13% in 2002.¹ This decline is likely related to changes in smoking patterns and habits in North America and Europe.² Although the incidence of SCLC is decreasing in the United States and Japan, it is unclear if the same holds true around the globe.^{1,3} Approximately two thirds of patients with SCLC are diagnosed with advanced disease.⁴ The remaining patients are diagnosed at a stage where their disease may be curable. This review focuses on the management of patients with limited-stage disease, a proportion of whom can be cured with aggressive multimodality therapy.

STAGING

Because systemic chemotherapy is the mainstay of treatment for all patients with SCLC, the main clinical purpose of staging is to determine whether thoracic irradiation should be incorporated in conjunction with chemotherapy for localized disease. Two systems are commonly used to stage SCLC: TNM classification,⁴ which

is identical to that used for non–small-cell lung cancer, and the Veterans Administration Lung Study Group limited disease–extensive stage system.

The International Association for the Study of Lung Cancer defines limited stage as absence of distant metastatic disease.⁵ According to this schema, limited-stage disease is confined to the ipsilateral hemithorax and contralateral mediastinal and supraclavicular nodes and ipsilateral pleural effusion (irrespective of whether cytology is positive), whereas extensive-stage disease includes disease in the contralateral hemithorax and distant metastases.

Despite this, the staging of patients with ipsilateral pleural effusion and supraclavicular node and contralateral mediastinal lymph node involvement is debated. Most trials for limited-stage disease tend to exclude patients with isolated pleural effusions,^{6,7} but survival of patients with isolated pleural effusions seems to be similar to that of other patients with limited-stage SCLC.⁸ Although older studies showed that supraclavicular lymph node involvement predicted slightly inferior survival,⁹ the International Association for

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ASSOCIATED CONTENT



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DOI: 10.1200/JOP.2015.009068

the Study of Lung Cancer staging project found no significant difference in outcome between N2 and N3 disease⁴; the greatest difference in outcome was between N1 and N2 nodal involvement.

MANAGEMENT

Initial Treatment

The current standard of care for limited-stage SCLC is chemotherapy and concurrent thoracic radiotherapy. This multimodality approach was proven superior to chemotherapy alone in the 1990s. A meta-analysis by Pignon et al¹⁰ examined 13 different trials that randomly assigned patients to chemotherapy or chemotherapy plus thoracic radiotherapy. In this analysis, there was a 5.4% improvement in overall survival (OS) at 3 years with the addition of thoracic radiotherapy.^{10,11}

Chemotherapy

SCLC is extremely chemosensitive,¹² with response rates of approximately 65%. Multiple agents with different mechanisms of action have shown activity against SCLC. These include platinum agents (cisplatin, carboplatin), camptothecins (topotecan, irinotecan), podophyllotoxins (etoposide), anthracyclines (doxorubicin, epirubicin, amrubicin), alkylating agents (cyclophosphamide, ifosfamide), taxanes (paclitaxel, docetaxel), and vinca alkaloids (vincristine).

Initial trials found high response rates with cyclophosphamide, doxorubicin, and vincristine (CAV) or cyclophosphamide, epirubicin, and vincristine.^{13,14} However, after the introduction of etoposide, the combination of etoposide with cisplatin (EP) demonstrated superior response rates compared with CAV.^{15,16} Also, EP was better tolerated and is thus the regimen of choice for initial treatment of SCLC.

The standard treatment regimen involves four to six cycles of chemotherapy with EP.¹⁷ However, benefit from this regimen seems mainly confined to patients younger than 55 years old, with increasing adverse outcomes in patients age 70 years or older.¹⁴ With cisplatin causing an increase in toxicity in the elderly, one could consider carboplatin in that population as an alternative.¹⁸

Thoracic radiotherapy

Chemotherapy alone results in poor local disease control, with 75% to 90% of patients developing intrathoracic failure.¹⁹ In contrast, thoracic radiotherapy can provide local control, because this disease is radiosensitive; however, thoracic

radiotherapy alone does not have a major impact on overall disease control.²⁰

Two meta-analyses concluded that a combination of thoracic radiotherapy and chemotherapy produced a small but definite improvement in survival. As described earlier, Pignon et al¹⁰ showed the addition of thoracic radiotherapy decreased the relative risk for death by 14% as compared with chemotherapy alone ($P = .001$). Another meta-analysis of 11 randomized trials also showed a 5.4% improvement in the 2-year survival rate with thoracic radiotherapy ($P < .05$).²¹

A Canadian population-based retrospective study found that combined-modality therapy improved median and 2-year survival as compared with chemotherapy alone (15.1 months and 32% v 14.3 months and 26.9%, respectively).²² Of note, when thoracic radiotherapy is administered, it is important that it be compliant with chemotherapy, or the survival benefit may be lost.²³

Even though the data support the use of a multimodality approach with chemotherapy and thoracic radiotherapy, the radiotherapy schedule and total radiation dose have been continuous sources of debate. Multiple studies have been conducted comparing early versus late thoracic radiotherapy (Table 1).^{6,7,23-27} Although the chemotherapy regimens and timing varied in these studies, the overall results were inconclusive.

Several meta-analyses have tried to answer this question, again with no definitive conclusion. Fried et al²⁸ showed a small but statistically significant benefit of early compared with late thoracic radiotherapy in terms of 2-year OS. This benefit was more pronounced when either hyperfractionated radiotherapy or platinum-based chemotherapy were used. However, another meta-analysis suggested that although there was no difference between early or late thoracic radiotherapy with regard to OS, there was a small but significant improvement in 5-year OS with early thoracic radiotherapy when only trials using platinum-based chemotherapy were considered (odds ratio, 0.64; 95% CI, 0.44 to 0.92; $P = .02$).²⁹ This was even more pronounced when the overall duration of thoracic radiotherapy was less than 30 days. A Cochrane review found no significant difference between approaches in 2- or 5-year survival.¹¹ These authors concluded that the effect of the timing of chest radiotherapy on survival was uncertain.

Another source of controversy is the optimal dose of radiation. A retrospective analysis of patients enrolled in three consecutive chemoradiotherapy trials, treated with 45, 55, or 65 Gy, found similar local control and OS. This suggested that a

Table 1. Timing of Thoracic Radiotherapy

First Author	Chemotherapy	Timing of Radiotherapy (No. of Patients)		Median OS (Months)		5-Year OS (%)	
		Early	Late	Early	Late	Early	Late
Perry ⁵	CAV+ etoposide	Day 1 (125)	Day 64 (145)	13	14.5	6.6	12.8
Work ⁷	CAV × 6/EP × 3 (radiotherapy with EP)	Day 1 (99)	Week 18 (100)	10.7	12.9	10	10
Skarlos ²⁴	Carboplatin and etoposide	Cycle 1 (42)	Cycle 4 (39)	17.5	17	22*	13*
Murray ²⁵	CAV/EP	Week 3 (155)	Week 15 (153)	21.2	16	22	13
Jeremic ²⁶	Carboplatin and etoposide (radiotherapy) + EP	Week 1 (52)	Week 6 (51)	34	26	30	15
Takada ²⁷	EP	Day 2 (114)	After cycle 4 (114)	27.2	19.7	23.7	18.3
Spiro ²³	CAV/EP	Cycle 2 (159)	Cycle 6 (166)	13.7	15.1	14*	19*

Abbreviations: CAV, cyclophosphamide, doxorubicin, and vincristine; EP, etoposide plus cisplatin; OS, overall survival.

*Three-year survival.

dose of at least 45 Gy would be needed to obtain adequate local control.³⁰ However, higher doses (56 to 60 Gy administered in a single daily fractionation scheme) have been shown to improve tumor control.^{31,32}

Hyperfractionated radiotherapy (twice daily) improves local control by applying higher doses of radiation administered in a shorter time. A randomized phase III trial that randomly assigned patients with limited-stage SCLC to either 1.8 Gy once daily over 5 weeks or accelerated 1.5 Gy twice daily for 3 weeks concurrent with four cycles of EP showed that patients receiving the accelerated twice-daily schedule had better median (23 v 19 months) and 5-year OS (26% v 16%) but had an increased incidence of grade 3 esophagitis or feeding tube placement (27% v 11%).³³ A criticism of this study has been that the two radiation doses used were not biologically equivalent.

A recent retrospective analysis using the National Cancer Database found that patients receiving radiation using three different fractionation schemes (45 Gy in 30 fractions, 70 Gy in 35 fractions, and 61.2 Gy in 34 fractions) had similar outcomes.³⁴ To answer this question, there are two phase III studies currently ongoing. The CALGB 30610/RTOG 0538 study (ClinicalTrials.gov identifier NCT00632853) by Cancer and Leukemia Group B and Radiation Therapy Oncology Group began as a three-arm study comparing hyperfractionated thoracic radiotherapy (1.5 Gy twice per day to a total dose of 45 Gy) versus 70 Gy in 2-Gy daily fractions versus 61.2-Gy concomitant boost thoracic radiotherapy. After a prespecified interim analysis, the concomitant boost arm

was stopped, and the study now compares hyperfractionated thoracic radiotherapy with 70 Gy administered in 2-Gy daily fractions. Another similar trial, CONVERT (Concurrent Once Daily Versus Twice Daily Radiotherapy for Limited Stage Small Cell Lung Cancer), conducted by the United Kingdom National Cancer Research Institute (ClinicalTrials.gov identifier NCT00433563), comparing standard thoracic radiotherapy (45 Gy at 1.5 Gy twice daily) with 70 Gy at 2-Gy daily thoracic radiotherapy with concurrent EP, has completed accrual, and results are pending. Until the results of these trials are available, both these approaches can be considered equivalent.

Surgical resection

Until recently, there has not been a role for surgery in the management of patients with SCLC. However, emerging data have suggested a role for surgical resection as part of multimodality therapy in limited-stage SCLC. A prospective study has reported 5-year survival rates up to 68%, typically in patients without nodal disease, with surgical resection.³⁵ Schreiber et al³⁶ reviewed the SEER database and found that patients with SCLC who underwent surgery had better survival for both localized and regional disease. This is especially promising because approximately 4% of lung cancers presenting as a solitary pulmonary nodule are SCLCs.³⁷ A study analyzing the SEER database noted 5-year survival rates of greater than 50% in patients with stage I disease who underwent a lobectomy.³⁸ Unfortunately,

details of systemic therapy are not available in these patients.

A recent retrospective analysis of 277 patients with limited-stage SCLC compared outcomes after surgical resection with those after conventional nonsurgical treatments.³⁹ Surgical resection was associated with significantly better 5-year survival in patients with clinical stage I disease (62% v 25%; $P < .01$). Although outcomes in patients with stage II or III disease were not significantly different, a propensity score–matched pair analysis of patients with stage II or III disease showed improved 5-year survival with surgical resection ($P = .04$).

Thus, patients with clinical stage T1-2 N0 disease are candidates for lobectomy. There are emerging data supporting a possible role for surgery in patients with N1 and possibly N2 disease, but this approach cannot be routinely recommended; it should be determined on a case-by-case basis. There is still a need for additional prospective studies that will help define the scope of surgical resection in the management of limited-stage SCLC.

Prophylactic Cranial Irradiation

The brain is a common site of metastasis in SCLC, and approximately 45% patients who achieve a complete response with initial therapy will present with brain metastases as the only site of relapse.⁴⁰

Two separate meta-analyses concluded that prophylactic cranial irradiation decreased the incidence of brain metastases by 52% to 54% and improved survival by 16% to 18% in patients who had achieved a complete response to therapy.^{41,42} In their meta-analysis of seven clinical trials in patients who were in complete remission after initial therapy, Aupérin et al⁴¹ showed a significant 3-year survival benefit in those who received prophylactic cranial irradiation (20.7% v 15.3%; $P = .01$). A retrospective analysis of North Central Cancer Treatment Group trials of prophylactic cranial irradiation in patients with stable disease or better showed that after induction therapy, the median OS increased from 14 to 17 months with prophylactic cranial irradiation ($P = .0045$).⁴³ In a retrospective SEER database analysis, which included 7,995 patients with limited-stage SCLC, Patel et al⁴⁴ showed an increase in 5-year survival with prophylactic cranial irradiation (19% v 11%; $P < .001$). On the basis of these results, standard practice now includes prophylactic cranial irradiation for patients with a complete (or good partial) response to initial therapy.

The optimal dose and fraction size for prophylactic cranial irradiation are unclear. A randomized trial compared a prophylactic cranial irradiation dose of 25 Gy in 10 fractions with high-dose prophylactic cranial irradiation (36 Gy in 18 fractions once daily or 36 Gy in 24 fractions using 1.5 Gy twice daily) in 720 patients with limited-stage SCLC who had achieved a complete response after chemotherapy and thoracic radiotherapy.⁴⁵ This study showed no significant reduction of brain metastases with higher-dose prophylactic cranial irradiation, but it did show a significant increase in mortality. Therefore, at the present time, prophylactic cranial irradiation at 25 Gy in 10 fractions should remain the standard of care.

One of the major concerns with the use of prophylactic cranial irradiation is long-term neurotoxicity. Studies have not shown a significant neurocognitive decline specifically attributable to prophylactic cranial irradiation.^{40,46} In a retrospective analysis of 98 patients, those who received prophylactic cranial irradiation had a significant improvement in mean Q-TWiST (quality time without symptoms and toxicity) survival.⁴⁷ In another similar analysis that evaluated quality-adjusted life expectancy, prophylactic cranial irradiation offered a benefit over no prophylactic cranial irradiation (mild toxicity, 4.31 and 3.70 quality-adjusted life-years; substantial toxicity, 4.09 and 3.70 quality-adjusted life-years, respectively).⁴⁸ The results of these analyses would suggest a benefit to prophylactic cranial irradiation without undue toxicity; however, well-designed clinical trials with this specific objective in mind are needed.

Relapsed or Refractory SCLC

Despite the excellent response rates seen initially, the majority of patients experience relapse; many of these are candidates for second-line treatment. Patients who relapse more than 3 months after the end of first-line treatment are considered chemotherapy sensitive.⁴⁹ Response rates to second-line therapy are approximately 25% in chemotherapy-sensitive patients, as opposed to approximately 10% in patients who have experience early relapse or have primary refractory disease.⁴⁹

Once patients experience relapse after initial therapy, the goal of treatment is mainly palliative. If disease is controlled for more than 6 months, a second course of EP can be considered.^{49,50} Topotecan, a water-soluble, semisynthetic derivative of camptothecin, has demonstrated antitumor activity in relapsed and refractory SCLC. In a randomized phase III study of 210 patients with sensitive relapse,

Table 2. Therapeutic Regimens

Modality	Schedule
First-line chemotherapy	Cisplatin 60 mg/m ² IV day 1; etoposide 120 mg/m ² /d IV days 1-3; repeat every 3 weeks
	Cisplatin 80 mg/m ² IV day 1; etoposide 100 mg/m ² /d IV days 1-3; repeat every 3-4 weeks
	Cisplatin 80 mg/m ² IV day 1; etoposide 80 mg/m ² /d IV days 1-3; repeat every 3 weeks
	Cisplatin 25 mg/m ² IV days 1-3; etoposide 80 mg/m ² /d IV days 1-3; repeat every 3-4 weeks
	Cisplatin 60 mg/m ² IV day 1; etoposide 120 mg/m ² /d IV days 1-3; repeat every 3 weeks
	Carboplatin AUC 5 IV day 1; etoposide 100 mg/m ² /d IV days 1-3; repeat every 4 weeks
	Carboplatin AUC 5 IV day 1; etoposide 80 mg/m ² /d IV days 1-3; repeat every 3-4 weeks
Thoracic radiotherapy	1.5 Gy twice daily (at least 6 hours apart) in 3 weeks for total dose of 45 Gy
	1.8 Gy daily over 6.5 weeks to total dose of at least 60 Gy
Prophylactic cranial irradiation	25 Gy in 10 daily fractions
	30 Gy in 10-15 daily fractions
	24 Gy in eight daily fractions
Relapsed disease	Topotecan 2.3 mg/m ² /d orally on days 1-5; repeat every 3 weeks
	Topotecan 1.5 mg/m ² /d IV on days 1-5; repeat every 3 weeks
	Amrubicin 40 mg/m ² /d IV on days 1-3; repeat every 3 weeks
	Paclitaxel 80 mg/m ² IV weekly for 6 weeks; repeat every 8 weeks
	Paclitaxel 175 mg/m ² IV day 1; repeat every 3 weeks
	Etoposide 50 mg/m ² orally daily for 21 days*; repeat every 4 weeks
	Docetaxel 100 mg IV day 1; repeat every 3 weeks
	Temozolomide 75 mg/m ² orally daily for 21 days*; repeat every 4 weeks

Abbreviation: IV, intravenously.

*Doses should be rounded to the nearest 50-mg dose.

topotecan improved time to progression and median survival compared with CAV.⁵¹ Moreover, topotecan had greater symptom control and decreased interference with daily activities. The oral formulation of topotecan seems to have similar efficacy.⁵²

Amrubicin, a synthetic 9-amino anthracycline, has shown promising activity in SCLC.⁵³ A phase III trial comparing amrubicin with topotecan in 637 patients found that although OS was similar, the subset of patients with refractory disease treated with amrubicin had better survival (6.2 v 5.7 months; $P = .047$).⁵³ Patients treated with amrubicin had significant symptom improvement, but they also had increased incidence of infection and febrile neutropenia. The common chemotherapy and radiation regimens used in the management of SCLC are summarized in [Table 2](#).

Multiple other agents, including taxanes, irinotecan, vinorelbine, temozolomide, bendamustine, and gemcitabine, have shown modest activity in relapsed and refractory SCLC. The programmed death-1 inhibitors pembrolizumab and nivolumab seem promising in initial studies.

OUTCOMES

Although the majority of patients with limited-stage SCLC experience relapse after initial treatment, there is a cohort of patients who can have long-term survival ([Fig 1](#)). Older studies have demonstrated a doubling of 5-year survival in these patients from 5% in 1973 to 10% in 1998.¹ A more recent analysis of the SEER database based on receipt of prophylactic cranial irradiation showed that 3-year OS for patients with limited-stage SCLC receiving prophylactic cranial irradiation

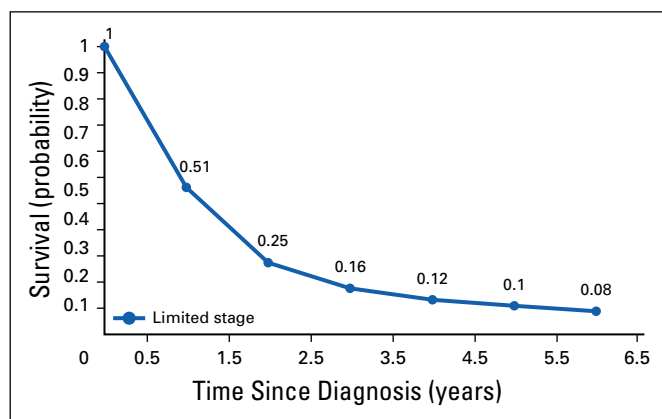


FIG 1. Survival of patients with limited-stage small-cell lung cancer.

was 23% compared with 17% for those not receiving prophylactic cranial irradiation.⁵⁴ Interestingly, when these patients were observed over time, 3-year conditional OS for patients alive at 1, 2, and 3 years after diagnosis was 23%, 39%, and 52%, respectively, suggesting that a proportion of patients could possibly be considered to have been cured of their disease.⁵⁴

In conclusion, combined-modality therapy is the mainstay of management of limited-stage SCLC. Concurrent chemotherapy with a combination of platinum and etoposide and thoracic radiotherapy should be recommended for all patients deemed fit for therapy. For patients who have extensive intrathoracic disease, it may be reasonable to administer two cycles of chemotherapy before starting radiotherapy. Surgical resection followed by adjuvant chemotherapy may benefit patients with early-stage disease. Prophylactic cranial irradiation has been shown to decrease the incidence of brain metastasis and improve OS in patients who do not experience progression during initial therapy. Multiple agents have shown modest activity in the second-line setting. **JOP**

Authors' Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

Author Contributions

Conception and design: Apar Kishor Ganti

Collection and assembly of data: All authors

Data analysis and interpretation: Kailash Mosalpuria, Apar Kishor Ganti

Manuscript writing: All authors

Final approval of manuscript: All authors

Corresponding author: Apar Kishor Ganti, MD, MS, Division of Oncology-Hematology, Department of Internal Medicine, University of Nebraska Medical Center, 987680 Nebraska Medical Center, Omaha, NE 68198-7680; e-mail: aganti@unmc.edu.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Multimodality Therapy for Limited-Stage Small-Cell Lung Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jop.ascopubs.org/site/misc/ifc.xhtml.

Daniel Almquist

No relationship to disclose

Kailash Mosalpuria

No relationship to disclose

Apar Kishor Ganti

Consulting or Advisory Role: Otsuka, Boehringer Ingelheim, Biodesix

Research Funding: Pfizer (Inst), Amgen (Inst), Newlink Genetics (Inst), ARIAD Pharmaceuticals (Inst), Astex Pharmaceuticals (Inst), Bristol-Myers Squibb (Inst), Merck Serono (Inst), Merck (Inst)