Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline

Charles M. Rudin
Nofisat Ismaila
Christine L. Hann
Narinder Malhotra
Benjamin Movsas

*Henry Ford Health System, BM0VSAS1@hfhs.org*

See next page for additional authors

Follow this and additional works at: [https://scholarlycommons.henryford.com/radiationoncology_articles](https://scholarlycommons.henryford.com/radiationoncology_articles)

**Recommended Citation**


This Article is brought to you for free and open access by the Radiation Oncology at Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Radiation Oncology Articles by an authorized administrator of Henry Ford Health System Scholarly Commons.
Authors
Charles M. Rudin, Nofisat Ismaila, Christine L. Hann, Narinder Malhotra, Benjamin Movsas, Kim Norris, M C. Pietanza, Suresh S. Ramalingam, Andrew T. Turrisi, and Giuseppe Giaccone

This article is available at Henry Ford Health System Scholarly Commons: https://scholarlycommons.henryford.com/radiationoncology_articles/261
Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline

Charles M. Rudin, Nofisat Ismaila, Christine L. Hann, Narinder Malhotra, Benjamin Movsas, Kim Norris, M. Catherine Pietanza, Suresh S. Ramalingam, Andrew T. Turrisi III, and Giuseppe Giaccone

ABSTRACT

Purpose
The American College of Chest Physicians (ACCP) produced an evidence-based guideline on treatment of patients with small-cell lung cancer (SCLC). Because of the relevance of this guideline to American Society of Clinical Oncology (ASCO) membership, ASCO reviewed the guideline, applying a set of procedures and policies used to critically examine guidelines developed by other organizations.

Methods
The ACCP guideline on the treatment of SCLC was reviewed for developmental rigor by methodologists. An ASCO Endorsement Panel updated the literature search, reviewed the content, and considered additional recommendations.

Results
The ASCO Endorsement Panel determined that the recommendations from the ACCP guideline, published in 2013, are clear, thorough, and based on current scientific evidence. ASCO endorses the ACCP guideline on the treatment of SCLC, with the addition of qualifying statements.

Recommendations
Surgery is indicated for selected stage I SCLC. Limited-stage disease should be treated with concurrent chemoradiotherapy in patients with good performance status. Thoracic radiotherapy should be administered early in the course of treatment, preferably beginning with cycle one or two of chemotherapy. Chemotherapy should consist of four cycles of a platinum agent and etoposide. Extensive-stage disease should be treated primarily with chemotherapy consisting of a platinum agent plus etoposide or irinotecan. Prophylactic cranial irradiation prolongs survival in patients with limited-stage disease who achieve a complete or partial response to initial therapy and may do so in similarly responding patients with extensive-stage disease as well. Additional information is available at http://www.asco.org/endorsements/sclc and http://www.asco.org/guidelineswiki.

J Clin Oncol 33:4106-4111. © 2015 by American Society of Clinical Oncology

INTRODUCTION
Small-cell lung cancer (SCLC) represents approximately 10% to 15% of all lung cancers.\textsuperscript{1,2} The incidence of SCLC in the United States has been steadily decreasing in the last two decades, mainly because of reduction in cigarette consumption, the primary cause of this tumor type.\textsuperscript{3} SCLC is characterized by rapid growth, early metastasis, and initial sensitivity to chemotherapy and radiotherapy.\textsuperscript{1,2} Unfortunately, despite initial response, patients with extensive disease develop drug resistance and die as a result of disease at a median of 10 to 12 months from diagnosis.\textsuperscript{1,2} In contrast, patients with limited disease can be successfully treated with combined concomitant chemoradiotherapy, which produces a 15% to 20% cure rate.\textsuperscript{4} The most important advances in the treatment of this disease in the last two decades have been based on improvements in application of radiotherapy.\textsuperscript{5} Chest irradiation and prophylactic brain irradiation have both been demonstrated to increase survival.\textsuperscript{6} However, few advances have been made in systemic treatment, with the last drug approved by the US Food and Drug Administration being topotecan in 1998.

The purpose of this American Society of Clinical Oncology (ASCO) guideline is to review and endorse the American College of Chest Physicians (ACCP) guideline on the treatment of SCLC by Jett et al\textsuperscript{5} published in \textit{Chest} in 2013. This ASCO endorsement reinforces the recommendations offered in the ACCP guideline and acknowledges the effort
ASCO Endorses the ACCP Clinical Practice Guideline on the Treatment of Small-Cell Lung Cancer, With Minor Qualifying Statements

Guideline Questions
1. In patients with small-cell lung cancer (SCLC), what is the ability of positron emission tomography (PET) imaging to determine the stage of cancer?
2. In patients with limited-stage (LS) SCLC, how do the parameters of thoracic radiotherapy (TRT) affect survival?
3. In patients with extensive-stage (ES) SCLC, what is the survival after treatment with chemotherapy, including novel and targeted agents?
4. In elderly patients with SCLC, what are survival and toxicity after treatment with chemotherapy or radiation therapy?

Target Population
Patients with SCLC

Target Audience
Primary care providers, oncologists, radiologists, pathologists, and other health providers

Methods
An American Society of Clinical Oncology (ASCO) Endorsement Panel was convened to consider endorsing the American College of Chest Physicians (ACCP) guideline recommendations on the treatment of SCLC, which were based on a systematic review of the medical literature. The ASCO Endorsement Panel considered the methodology employed in the ACCP guideline using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) review instrument. The ASCO Endorsement Panel carefully reviewed the ACCP guideline content to determine appropriateness for ASCO endorsement.

ASCO Key Recommendations for Treatment of SCLC
ASCO qualifying statements appear in bold italics (with remarks shown in italics). Data Supplement 1 provides a reprint of all the ACCP recommendations.

- In patients with SCLC (proven or suspected), a staging evaluation is recommended consisting of a medical history and physical examination, CBC and comprehensive chemistry panel with renal and hepatic function tests, CT [computed tomography] of the chest and abdomen with intravenous contrast or CT scan of the chest extending through the liver and adrenal glands, MRI [magnetic resonance imaging] or CT of the brain, and bone scan (grade 1B). If PET is obtained, then bone scan may be omitted. CBC should include differential.

- In patients with clinically LS SCLC, PET imaging is suggested (grade 2C). Remark: If PET is obtained, then bone scan may be omitted. PET scan use is also applicable to ES SCLC.

- In patients with SCLC, it is recommended that both the Veterans’ Administration system (LS v ES) and the American Joint Committee on Cancer/International Union Against Cancer seventh edition system (TNM) should be used to classify the tumor stage (grade 1B).

- In patients with clinical stage I SCLC, who are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head MRI/CT and PET or abdominal CT plus bone scan) are recommended (grade 1B).

- In patients with clinical stage I SCLC, after a thorough evaluation for distant metastases and invasive mediastinal stage evaluation, surgical resection is suggested over nonsurgical treatment (grade 2C).

- In patients with stage I SCLC who have undergone curative-intent surgical resection, platinum-based adjuvant chemotherapy is recommended (grade 1C).

(continued on following page)
THE BOTTOM LINE (CONTINUED)

- In patients with LS SCLC, early chemoradiotherapy, with accelerated hyperfractionated radiation therapy (twice-daily treatment) concurrently with platinum-based chemotherapy, is recommended (grade 1B). Comparison of accelerated hyperfractionated radiotherapy with an extended course of daily radiation therapy at standard fractionation is currently being investigated.

- In patients with LS or ES SCLC who achieve a complete or partial response to initial therapy, prophylactic cranial irradiation (PCI) is recommended (grade 1B). Remark: The regimen of 25 Gy in 10 daily fractions has the greatest supporting data for safety and efficacy. The panel notes that a recent Japanese study failed to demonstrate survival advantage with PCI in patients with ES SCLC. On publication of the mature data from this study, the recommendation for PCI in ES SCLC might be subject to revision.

- In patients with ES SCLC who have completed chemotherapy and achieved a complete or partial response in the chest, a course of consolidative TRT is suggested (grade 2C). Further evaluation of this question is required before a treatment recommendation can be made.

- In patients with either LS or ES SCLC, four to six cycles of platinum-based chemotherapy with either cisplatin or carboplatin plus either etoposide or irinotecan are recommended over other chemotherapy regimens (grade 1A). Clinical trials in the United States and Europe have not demonstrated a benefit for the irinotecan regimen over that based on etoposide. In LS disease, four cycles is preferred.

- In patients with relapsed or refractory SCLC, the administration of second-line, single-agent chemotherapy is recommended (grade 1B). Remark: Reinitiation of the previously administered first-line chemotherapy regimen is recommended in patients who experience relapse 6 months from completion of initial chemotherapy. Enrollment onto a clinical trial is encouraged. Single-agent topotecan has US Food and Drug Administration approval in this context.

- In elderly patients with LS SCLC and good performance status (PS; Eastern Cooperative Oncology Group [ECOG] 0 to 2), treatment with platinum-based chemotherapy plus TRT is suggested, with close attention to management of treatment-related toxicity (grade 2B).

- In elderly patients with ES SCLC and good PS (ECOG 0 to 2), treatment with carboplatin-based chemotherapy is suggested (grade 2A).

- In elderly patients with SCLC and poor PS, treatment with chemotherapy is suggested if the poor PS is due to SCLC (grade 2C).

Additional Resources
More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at http://www.asco.org/endorsements/sclc and http://www.asco.org/guidelineswiki. Patient information is available at http://www.cancer.net.

A link to the ACCP guideline recommendations on treatment of SCLC can be found at http://www.chestnet.org/.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

put forth by the ACCP to produce an evidence-based guideline informing practitioners who care for patients with SCLC. The issues addressed in the original guideline as well as this endorsement concern the diagnosis and management of patients with SCLC. A reprint of all the ACCP recommendations is provided in Data Supplement 2 and online at http://journal.publications.chestnet.org/article.aspx?articleID=1685799#SummaryofRecommendations.

OVERVIEW OF ASCO GUIDELINE ENDORSEMENT PROCESS

ASCO has policies and procedures for endorsing practice guidelines that have been developed by other professional organizations. The goal of guideline endorsement is to increase the number of high-quality, ASCO-vetted guidelines available to the ASCO membership. The ASCO endorsement process involves an assessment by ASCO staff of candidate guidelines for methodologic quality using the Rigour of Development subscale of the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument (details provided in Methodology Supplement).

Disclaimer
The clinical practice guideline and other guidance published herein are provided by ASCO to assist providers in making clinical decisions. The information herein should not be relied on as being
complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified herein and is not applicable to other interventions, diseases, or stages of disease. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, because the information does not account for individual variation among patients. Each recommendation reflects high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual patient cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an as-is basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

Guideline and Conflicts of Interest

The ASCO Expert Panel (members listed in Appendix Table A1, online only) was assembled in accordance with the ASCO Conflicts of Interest Management Procedures for Clinical Practice Guidelines (summarized at http://www.asco.org/rwc). Members of the panel completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speaker’s bureau; research funding; patents, royalties, and other intellectual property; expert testimony; travel, accommodations, and expenses; and other relationships. In accordance with these procedures, the majority of the members of the panel did not disclose any such relationships.

CLINICAL QUESTIONS AND TARGET POPULATION

An electronic search strategy of the literature performed in constructing the ACCP guideline focused on four principal questions: (1) In patients with SCLC, what is the ability of positron emission tomography (PET) imaging to determine the stage of cancer? (2) In patients with limited stage (LS) SCLC, how do the parameters of thoracic radiotherapy (TRT) affect survival? (3) In patients with extensive-stage (ES) SCLC, what is the survival after treatment with chemotherapy, including novel and targeted agents? (4) In elderly patients with SCLC, what is the survival and toxicity after treatment with chemotherapy or radiotherapy? The target population for the ACCP guideline is patients with SCLC.

SUMMARY OF SCLC TREATMENT GUIDELINE DEVELOPMENT METHODOLOGY

The ACCP guideline was developed by an author expert panel and a scientific advisory panel that included experts in oncology, pathology, and methodology. The literature search of MEDLINE, Embase, and five Cochrane databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Health Technology Assessment, and National Health Service Economic Evaluation Database) spanned 2004 through 2011. The search included all levels of evidence (randomized controlled trials [RCTs] and observational studies) as long as they appeared in peer-reviewed publications, the minimal threshold. Details of the search strategies and study inclusion criteria and outcomes of interest are available at http://journal.publications.chestnet.org/data/Journals/CHEST/926876/chest_143_5_suppl_e4005.pdf. The searches identified studies for inclusion in the guideline qualitative synthesis of the literature. The ACCP panel reviewed RCTs as well as observational studies.

RESULTS OF ASCO METHODOLOGY REVIEW

The methodology review of the ACCP guideline was completed independently by two ASCO guideline staff members using the Rigour of Development subscale from the AGREE II instrument. Detailed results of the scoring for this guideline are available on request to guidelines@asco.org. Overall, the ACCP guideline on treatment of SCLC scored 89% on the Rigour subscale. The methodology was not described in detail in the actual guideline but rather in supplementary material that covered other topics on diagnosis and management of lung cancer. The preliminary ASCO content reviewers of the treatment of SCLC guideline as well as the ASCO Endorsement Panel found the recommendations well supported in the original guideline. Each section, including introduction, methods, results, and recommendations sections, was clear and well referenced from the systematic review.

METHODS AND RESULTS OF ASCO UPDATED LITERATURE REVIEW

ASCO guidelines staff updated the ACCP guideline on treatment of SCLC literature search. Using the Ovid platform, the following databases were searched from 2011 to March 2015: Medline, Embase, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, Cochrane Central Register of Trials, Health Technology Assessments Database, and National Health Service Economic Evaluations Database. The search was restricted to articles published in English and to systematic reviews, meta-analyses, and RCTs.

The updated search yielded 1,169 articles. A review of these results revealed no definitive evidence that would warrant substantive modification of the treatment of SCLC practice recommendations. The committee did wish to clarify or comment on some areas of recent controversy and ongoing research.
The ASCO Endorsement Panel reviewed the ACCP guideline on treatment of SCLC and concurs that the recommendations are clear, thorough, and based on relevant scientific evidence in this content area and present options that will be acceptable to patients and clinicians. Overall, the ASCO Endorsement Panel agrees with the recommendations as stated in the guideline. The grading system and remarks were left as is, but the panel included several qualifying statements. Details of the ACCP grading system can be found in Data Supplement 3.

**RESULTS OF ASCO CONTENT REVIEW**

The ASCO Endorsement Panel wants to highlight and qualify some of the statements from the ACCP guideline on the treatment of SCLC. Overall, the panel was in agreement with the 14 recommendation statements included in the ACCP guideline. However, the panel believed it would be beneficial to include qualifying statements to six of these recommendations. The areas of concern are discussed as follows:

**PET Scanning in SCLC**

There was overall consensus that in patients with SCLC, a staging evaluation should be performed, which should include a medical history and physical examination, CBC and comprehensive chemistry panel with renal and hepatic function tests, computed tomography (CT) scan of the chest and abdomen with intravenous contrast or CT scan of the chest extending through the liver and adrenal glands, magnetic resonance imaging or CT of the brain, and bone scan. However, the panel recognizes that PET scanning has become increasingly widely used initial staging tool in patients with lung cancer. If a PET scan is obtained, a bone scan may then be omitted. In addition, when obtaining the CBC, the differential should be included. These qualifying statements apply to patients with both LS and ES disease.

**TRT Schedule in LS SCLC**

The use of early chemoradiotherapy, with accelerated hyperfractionated radiation therapy (twice-daily treatment) concurrently with platinum-based chemotherapy, in patients with LS SCLC is recommended. The panel wishes to remind the oncology community that there are ongoing studies comparing accelerated hyperfractionated radiotherapy with an extended course of daily radiation therapy at standard once-daily fractionation (ClinicalTrials.gov identifier NCT00632853). This recommendation may need to be revisited when results from these studies are published.

**Consolidative TRT in ES SCLC**

In patients with ES SCLC who have completed chemotherapy and achieved a complete response outside the chest and complete or partial response in the chest, a course of consolidative TRT is suggested. The panel raised some concerns with regard to the strength of the available evidence on this topic. They agreed that further evaluation of this question is needed before an actionable recommendation can be made and noted that additional studies are in progress.

**Choice and Duration of First-Line Chemotherapy**

Four to six cycles of platinum-based chemotherapy with either cisplatin or carboplatin plus either etoposide or irinotecan are recommended over other chemotherapy regimens in patients with either LS or ES SCLC. The panel noted that clinical trials in the United States and Europe have not demonstrated a benefit for the irinotecan regimen over that containing etoposide. The panel also agreed that in LS disease, four cycles of platinum-based chemotherapy are preferred.

---

**REFERENCES**


---

**ENDORSEMENT RECOMMENDATION**


**ADDITIONAL RESOURCES**

More information, including a Data Supplement with a reprint of all treatment of SCLC recommendations (original guideline), a Methodology Supplement, slide sets, and clinical tools and resources, is available at <http://www.asco.org/endorsements/sclc> and <http://www.asco.org/guidelineswiki>. Patient information is available at <http://www.cancer.net>.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Disclosures provided by the authors are available with this article at <www.jco.org>.

**AUTHOR CONTRIBUTIONS**

Administrative support: Nofisat Ismaila

Manuscript writing: All authors

Final approval of manuscript: All authors

© 2015 by American Society of Clinical Oncology

Downloaded from ascopubs.org by Henry Ford Hospital on December 13, 2019 from 150.198.017.009

Copyright © 2019 American Society of Clinical Oncology. All rights reserved.


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline

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 jco.ascopubs.org/site/ifc.

Charles Rudin
Consulting or Advisory Role: Boehringer Ingelheim, GlaxoSmithKline, Merck, Celgene
Research Funding: Biomarin

Nofsat Ismaila
Employment: GlaxoSmithKline (I)
Stock or Other Ownership: GlaxoSmithKline (I)
Travel, Accommodations, Expenses: GlaxoSmithKline (I)

Christine Hann
Research Funding: GlaxoSmithKline (Inst), GlaxoSmithKline (Inst), Bristol-Myers Squibb (I), Gilead Sciences (I)

Narinder Malhotra
Employment: Wexford Health Source, Correct Care Solutions

Benjamin Movsas
Research Funding: Varian Medical Systems (Inst), Philips Healthcare (Inst)
Patents, Royalties, Other Intellectual Property: Lung phantom for image guidance, MR-CT imaging–related patent for radiation oncology
Travel, Accommodations, Expenses: Varian Medical Systems

Kim Norris
Honoraria: Novartis

Consulting or Advisory Role: Novartis
Travel, Accommodations, Expenses: Novartis, Genentech

M. Catherine Pietanza
Honoraria: Genentech, Celgene
Consulting or Advisory Role: Genentech, Celgene
Speakers’ Bureau: Quintiles, PER
Research Funding: Novartis (Inst), Stem CentRx (Inst), OncoMed Pharmaceuticals (Inst), Bristol-Myers Squibb (Inst)

Suresh Ramalingam
Consulting or Advisory Role: Boehringer Ingelheim, Celgene, Novartis, Genentech/Roche, Eli Lilly/ImClone, Bristol-Myers Squibb, AstraZeneca, Abbvie
Travel, Accommodations, Expenses: EMD Serono, Pfizer, AstraZeneca

Andrew Turrisi
Employment: Delta-Medix
Consulting or Advisory Role: Care Core National

Giuseppe Giaccone
Consulting or Advisory Role: Boehringer Ingelheim, Clovis Oncology, Celgene
Research Funding: Karyopharm Therapeutics
Acknowledgment

The American Society of Clinical Oncology (ASCO) Endorsement Panel thanks James Frame, MD, Eric Mininberg, MD, and the ASCO Clinical Practice Guidelines Committee for their thoughtful reviews of and insightful comments on this guideline endorsement.

Appendix

Table A1. ASCO Treatment of SCLC Endorsement Panel

<table>
<thead>
<tr>
<th>Member</th>
<th>Affiliation/Institution</th>
<th>Role/Area of Expertise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giuseppe Giaccone (co-chair)</td>
<td>Georgetown University, Washington, DC</td>
<td>Medical oncologist</td>
</tr>
<tr>
<td>Charles M. Rudin (co-chair)</td>
<td>Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY</td>
<td>Medical oncologist</td>
</tr>
<tr>
<td>Suresh S. Ramalingam</td>
<td>Emory University, Atlanta, GA</td>
<td>Medical oncologist</td>
</tr>
<tr>
<td>Christine L. Hann</td>
<td>John Hopkins University, Baltimore, MD</td>
<td>Medical oncologist</td>
</tr>
<tr>
<td>M. Catherine Pietanza</td>
<td>Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY</td>
<td>Medical oncologist</td>
</tr>
<tr>
<td>Benjamin Movsas</td>
<td>Henry Ford Hospital, Detroit, MI</td>
<td>Radiation oncologist</td>
</tr>
<tr>
<td>Andrew T. Turrisi III</td>
<td>DeltaMedix, Scranton, PA</td>
<td>Radiation oncologist</td>
</tr>
<tr>
<td>Narinder Malhotra</td>
<td>Correct Care Solutions, Pittsburgh, PA</td>
<td>Patient guideline implementation network representative</td>
</tr>
<tr>
<td>Kim Norris</td>
<td>Lung Cancer Foundation of America, Marina del Rey, CA</td>
<td>Patient representative</td>
</tr>
</tbody>
</table>

Abbreviations: ASCO, American Society of Clinical Oncology; SCLC, small-cell lung cancer.