CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Treatment of Small Cell Lung Cancer

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **Small cell lung cancer (SCLC) is a lethal disease for which there have been only small advances in diagnosis and treatment in the past decade. Our goal was to revise the evidence-based guidelines on staging and best available treatment options.**

Methods: **A comprehensive literature search covering 2004 to 2011 was conducted in MEDLINE, Embase, and five Cochrane databases using SCLC terms. This was cross-checked with the authors' own literature searches and knowledge of the literature. Results were limited to research in humans and articles written in English.**

Results: **The staging classification should include both the old Veterans Administration staging classification of limited stage (LS) and extensive stage (ES), as well as the new seventh edition American Joint Committee on Cancer/International Union Against Cancer staging by TNM. The use of PET scanning is likely to improve the accuracy of staging. Surgery is indicated for carefully selected stage I SCLC. LS 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 1 or 2 of chemotherapy. Chemotherapy should consist of four cycles of a platinum agent and etoposide. ES disease should be treated primarily with chemotherapy consisting of a platinum agent plus etoposide or irinotecan. Prophylactic cranial irradiation prolongs survival in those individuals with both LS and ES disease who achieve a complete or partial response to initial therapy. To date, no molecularly targeted therapy agent has demonstrated proven efficacy against SCLC.**

Conclusion: **Evidence-based guidelines are provided for the staging and treatment of SCLC. LS-SCLC is treated with curative intent with 20% to 25% 5-year survival. ES-SCLC is initially responsive to standard treatment, but almost always relapses, with virtually no patients surviving for 5 years. Targeted therapies have no proven efficacy against SCLC.**

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Abbreviations: ACCP = American College of Chest Physicians; ACE = doxorubicin, cyclophosphamide, and etoposide; BED = biologically effective dose; CAV = cyclophosphamide, doxorubicin, and vincristine; CR = complete response; ECOG = Eastern Cooperative Oncology Group; EP = etoposide plus cisplatin; ES = extensive stage; FDG = ^{18}F-fluorodeoxyglucose; Gy = Gray; HR = hazard ratio; IASLC = International Association for the Study of Lung Cancer; IP = irinotecan and cisplatin; LS = limited stage; MST = median survival time; NCCTG = North Central Cancer Treatment Group; PCI = prophylactic cranial irradiation; PS = performance status; RT = radiation therapy; SCLC = small cell lung cancer; SEER = Surveillance Epidemiology and End Results; SER = start of any treatment and the end of thoracic radiotherapy; TEP = treatment with etoposide plus cisplatin;TRT = thoracic radiotherapy; VALSG = Veterans Administration Lung Study Group

Summary of Recommendations

2.4.1 In patients with small cell lung cancer (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 of the chest and abdomen with intravenous contrast or CT scan of the chest extending through the liver and adrenal glands, MRI or CT of the brain, and bone scan (Grade 1B)**.**

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2.4.2. In patients with clinically limited-stage (LS)-SCLC, PET imaging is suggested (Grade 2C).

Remark: If PET is obtained, then bone scan may be omitted.

2.4.3. In patients with SCLC, it is recommended that both the Veterans Administration system (LS vs extensive stage [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).

3.1.1. 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) is recommended (Grade 1B).

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

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

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4.3.1. In patients with LS-SCLC, early chemoradiotherapy, with accelerated hyper-fractionated radiation therapy (twice-daily treatment) concurrently with platinum-based chemotherapy, is recommended (Grade 1B).

4.3.2. In patients with LS- or ES-SCLC who achieve a complete or partial response to initial therapy, prophylactic cranial irradiation is recommended (Grade 1B).

Remark: The regimen of 25 Gy in 10 daily fractions has the greatest supporting data for safety and efficacy.

4.3.3. 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 thoracic radiotherapy (TRT) is suggested (Grade 2C).

6.1.1. 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 is recommended over other chemotherapy regimens (Grade 1A).

7.1.1. 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 relapse > 6 months from completion of initial chemotherapy. Enrollment in a clinical trial is encouraged.

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

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

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

The National Cancer Institute Surveillance Epidemiology and End Results (SEER) database reports that small cell lung cancer (SCLC) currently accounts for 13.6% of all lung cancers.[2] SCLC is generally a

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rapidly growing cancer with a tendency for early metastases. To date, no study has suggested any beneficial role of screening with low-dose CT scans for SCLC.[3]

This document represents an evidence-based guideline based on a literature review that covered material since 2004, which overlaps the last American College of Chest Physicians (ACCP) literature review for the 2007 guidelines. Since the publication of the 2007 guidelines, there have been limited changes in diagnosis and staging for SCLC and no substantial changes in treatment of or improvement in survival from this disease. The median survival for limited-stage (LS) disease is 18 to 24 months with a 5-year survival of 20% to 25%. For extensive-stage (ES) disease, the median survival is 9 to 10 months, with $<10\%$ of patients alive at 2 years. Many new drugs have been tested in patients with SCLC, with mostly negative results. To date, no molecularly targeted therapy has demonstrated a benefit in SCLC.

1.0 Methods

To identify relevant studies, a team of research librarians and authors conducted a comprehensive literature search using SCLC terms and an adapted therapy hedge from MEDLINE's Clinical Queries, optimized for sensitivity.[4] The search was conducted in 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 NHS Economic Evaluation Database). Results were limited to human and English-language abstracts and articles published from 2004 to 2011. The search done for the 2007 guidelines was through March 2005, so this current search overlapped the previous guidelines search by approximately 1 year. The search strategy and results are available on request. The search was structured around the following patient, intervention, comparator, outcome (PICO) questions:

1. In patients with SCLC, what is the ability of PET imaging to determine the stage of cancer?
2. In patients with LS-SCLC, how do the parameters of thoracic radiotherapy (TRT) affect survival?
3. In patients with 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 radiation?

2.0 Staging of SCLC

2.1 Staging Systems

The Veterans Administration Lung Study Group (VALSG) two-stage classification scheme has been used routinely for the clinical staging of SCLC.[5] The VALSG system defines LS disease as (1) disease confined to one hemithorax, although local extension may be present; (2) no extrathoracic metastases except for ipsilateral supraclavicular lymph nodes; and (3) primary tumor and regional nodes that can be encompassed adequately in a reasonably safe radiation portal. ES disease is defined as disease that cannot be classified as LS disease, including malignant pleural or pericardial effusions, contralateral hilar or supraclavicular lymph nodes, and hematogenous metastases. In 1989, the International Association for the Study of Lung Cancer (IASLC) proposed a modified staging system in which LS was expanded to include contralateral mediastinal or supraclavicular lymph node metastases and ipsilateral pleural effusions independent of cytology.[6] A single-institution retrospective review of 109 patients with SCLC suggested that the IASLC staging system had better prognostic discrimination than the VALSG scheme.[7] In practice, most physicians and clinical trials blend the VALSG and IASLC criteria by considering contralateral mediastinal and ipsilateral supraclavicular lymph node involvement to be LS. Determining the classification of contralateral supraclavicular or hilar lymph node involvement remains controversial, with treatment usually determined individually based on the ability to include these regions in a safe radiotherapy port.

Recently, it has been proposed that the newly revised TNM staging classification for lung cancer (American Joint Committee on Cancer seventh edition)[8] should replace the VALSG system for the staging of SCLC. This recommendation is based on a prognostic analysis of 8,088 patients with SCLC in the IASLC database.[9,10] In clinically staged patients without hematogenous metastases, both the cT and cN descriptors were discriminatory for overall survival (both $P<.0001$), although there was no significant difference between cN0 and cN1.[9] The overall clinical stage I to IV groupings were also predictive of overall survival, and this finding was validated in a cohort of 4,884 patients with SCLC from the SEER registry.[9] Interestingly, the survival rates of patients with pleural effusions, but otherwise LS disease, were intermediate between those of patients with LS without effusion and patients with ES, regardless of pleural fluid cytology. There were insufficient data to determine the prognostic impact of contralateral supraclavicular lymph node involvement compared with ipsilateral supraclavicular or contralateral mediastinal lymph node involvement. A separate analysis of 349 patients in the IASLC database with SCLC pathologically staged by complete (R0) resection also demonstrated the prognostic impact of the T and N classifiers.[10] Using the American Joint Committee on Cancer seventh edition TNM system, the pathologic stage I to IV groupings also correlated with overall survival, although only the differences between stages II and III, and III and III, achieved statistical significance.[10] Independently, an analysis of 10,660 patients

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with SCLC from the California Cancer Registry confirmed the prognostic value of the T and N classifiers, as well as the overall stage I to IV groupings.[11]

These retrospective studies support the applicability of TNM staging to SCLC. However, the degree of prognostic discrimination in SCLC was less impressive than that seen for non-SCLC,[8] and, because the vast majority of clinical trials in SCLC have used the VALSG staging system, it is unlikely that the application of TNM staging would significantly alter clinical decision-making in the near future. Nevertheless, TNM staging is useful in the selection of patients for surgical resection (ie, T1-2 N0) and should be implemented in clinical trial stratification and in tumor registry accession to allow future refinement of appropriate therapeutic options. The TNM equivalent of LS-SCLC is T any, N any, and M0 (except T3-4 because of multiple lung nodules), whereas the TNM equivalent of ES-SCLC is T any, N any, M1a/b, or T3-4 because of multiple lung nodules.

2.2 Staging Workup

The initial evaluation of patients with newly diagnosed SCLC consists of a complete medical history and physical examination, a pathologic review of biopsy specimens, and laboratory studies, including CBC, serum electrolytes, renal and liver function tests, and serum lactate dehydrogenase. Because LS-SCLC is a curable disease, the most important issue in staging is to determine whether there are any distant metastases. Routine procedures to identify metastatic disease include contrast-enhanced CT scans of the chest and abdomen, bone scan, and MRI or CT scan of the brain. MRI scans detect brain metastases in 10% to 15% of asymptomatic patients with SCLC at initial diagnosis, including 12% of patients with otherwise LS-SCLC.[12,13] Bone marrow aspiration and biopsy can detect metastatic SCLC cells in 15% to 30% of patients at diagnosis.[14-16] However, $<5\%$ of patients will have bone marrow involvement as the only site of metastatic disease.[14-16] Therefore, routine bone marrow examination is not indicated and should be reserved for patients with peripheral cytopenia and no other evidence of metastatic disease.

2.3 PET Scan in SCLC

The use of PET scans in the initial staging of patients with SCLC has been evaluated in 13 studies comparing pretreatment ^{18}F-fluorodeoxyglucose (FDG)-PET scanning with conventional staging procedures (Fig 1).[17-29] These studies have been relatively small (range, 7-120 patients), comprising a total of 466 patients. Five studies were prospective (n = 209)[17-21] and eight were retrospective (n = 257).[22-29] Study designs varied with regard to the extent of conventional staging, the use of PET scans alone or PET/CT scans, and the method used to define PET scan positivity. In addition, some studies required a biopsy of all FDG-avid lesions that would alter stage, whereas others used further imaging studies or clinical follow-up to confirm PET scan findings. Several studies did not require any validation of PET scan findings or stage alterations.

FIGURE 1. Staging of SCLC: PET or PET/CT scans compared with conventional imaging.

Study	No. All	No. LS/ES	PET or PET/CT	% Stage concordance	How were discordant lesions confirmed?	Up-staged (%) [LS→ES]	Down-staged (%) [ES→LS]
Prospective (5)							
Brink 2004[17]	120	51/69	PET	88[a]	H, I	20	4
Bradley 2004[18]	24	24/0	PET	88[b]	I, U	8	----
Chin 2002[19]	18	9/9	PET	83	I, CC	22	11
Kut 2007[20]	18	6/12	PET	100	I, CC	0	0
Fischer 2007[21]	29	9/20	PET/CT	83[c]	I, CC	33	5
Subtotal	209	99/110		88		17%	5
Retrospective (8)							
Vinjamuri 2008[22]	51	18/33	PET	80[d]	H, I, CC	6	18
Azad 2010[23]	46	26/20	PET	74	H, I, CC, U	15	40
Schumacher 2001[24]	26	13/13	PET	73	H, I, CC, U	54	0
Shen 2002[25]	25	10/15	PET	92	H, I	10	7
Blum 2004[26]	15	15/0	PET	67	I, CC U	33	----
Hauber 2001[27]	7	6/1	PET	100	-----	0	0
Niho 2007[28]	63	63/0	PET + PET/CT	92	I, CC	8	----
Kamel 2003[29]	24	17/7	PET + PET/CT	83	H, I, U	18	14
Subtotal	257	168/89		82		15	18
Total	**466**	**267/199**		**85**		**16**	**11**

CC = confirmation by clinical course; ES = extensive stage; H = histologic confirmation; I = imaging confirmation; LS = limited stage; SCLC = small cell lung cancer; U = unconfirmed.

[a]One false-negative PET scan finding.

[b]One false-positive PET scan finding.

[c]One equivocal finding.

[d]One false-positive and two false-negative PET scan findings.

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SCLC is a highly metabolic malignancy, leading to a sensitivity of 100% for PET scan detection of primary tumors.[17,18,24,25,27] Overall, cumulative staging concordance was 85% between PET scan and conventional imaging,[17-20,22-29] with better concordance noted in the prospective (89%; range, 83%-100%) than in the retrospective (82%; range, 67%-100%) studies. Of the 267 patients with LS-SCLC by conventional imaging, 16% were upstaged to ES by PET scan, with similar findings in the prospective (17%; range, 0%-33%) and retrospective (15%; range, 0%-54%) studies.[17-20,22-29] Of the 199 patients whose ES-SCLC was diagnosed by conventional imaging, 11% were downstaged to LS by PET scan, with a much lower percentage of downstaged patients noted in the prospective (5%; range, 0%-11%) than in the retrospective (18%; range, 0%-40%) studies.[17,19,20,22-25,27,29] For most metastatic sites, PET scan was superior to standard imaging in both sensitivity and specificity.[17,18,24,25,27] However, PET scan was inferior to MRI or CT scan for the detection of brain metastases.[17,28]

Seven studies, three prospective[18,20,30] and four retrospective,[23,26,29,31] evaluated changes in management based on PET scan in patients with SCLC (Fig 2). Overall, PET scan findings led to a change in initial management in 28% (range, 0%-47%) of the 211 patients included in these studies. One-third of these changes were due to alterations in the general treatment plan due to stage shift, while the remaining two-thirds were due to changes in the radiation field in patients with LS-SCLC. One of these studies found that only 3% of patients who underwent PET scan-guided radiation planning had isolated nodal failure, compared with 11% of historical control patients who underwent CT scan-guided radiation planning, suggesting some improvement in locoregional disease control with the use of PET scan.[30]

Three retrospective studies assessed the use of PET scan in the restaging of SCLC after initial therapy.[24,25,29] Lack of uniform data analysis makes it impossible to combine study findings, but in general, 20% to 25% of patients were found to have more disease and 23% to 38% less disease by PET scan,[24,26,29] and 29% of patients had a change in management based on PET scan findings (Fig 2).[24,26,29] Three small prospective studies (total n = 36) evaluated the use of PET scan in response assessment in SCLC.[32-34] Variations in technical and analytic methods limit the ability to compile data from these studies. All three studies noted that metabolic response on both early (after one cycle of chemotherapy) and final (after completion of therapy) PET scans correlated highly with response criteria per final CT scan. None of these trials could determine if response assessment by PET scan added any benefit in patients with SCLC.

The prognostic value of PET scans in SCLC has been evaluated in four studies.[26,35-37] One prospective study of 76 patients with both LS- and ES-SCLC reported a significant association between pretreatment FDG-uptake level and both progression-free and overall survival.[35] Three retrospective studies comprising 93 patients demonstrated that patients with a complete response (CR) on posttreatment PET scan had significantly better progression-free and overall survival.[16,36,37]

Overall, the use of PET scans, in addition to CT scans of the chest and abdomen and MRI or CT scans of the brain, appears to improve the accuracy of initial staging and radiotherapy planning in patients with SCLC. However, further well-designed, prospective trials with pathologic confirmation of imaging findings are still needed to fully define the impact of PET scans on the outcome of patients with SCLC. If a PET scan is obtained for initial staging, pathologic confirmation

FIGURE 2. Change in management of SCLC based on PET scan findings.

Study	No.	PET or PET/CT	How were discordant lesions confirmed?	% Change in Management	% Change in RT Field	% Change in Treatment
INITIAL PET - Prospective						
Bradley 2004[18]	24	PET	I, U	33	29	4
Kut 2007[20]	21	PET	I, CC	0	-	0
Van Loon 2010[31]	60	PET/CT	U	30	30	-
Retrospective						
Azad 2010[23]	46	PET	H, I, CC, U	26	7	20
Van Loon 2008[32]	21	PET	U	24	24	-
Blum 2004[26]	15	PET	I, CC, U	47	13	33
Kamel 2003[29]	24	PET + PET/CT	H, I, U	37	21	17
Total	211			28	21	15
RESTAGING PET - Retrospective						
Blum 2004[26]	25	PET	I, CC, U	40	----	40
Kamel 2003[29]	20	PET + PET/CT	H, I, U	15	----	15
Total	45			29	----	29

RT = radiation therapy. See Figure 1 for expansion of other abbreviations.

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is required for lesions that result in upstaging. If a patient already has documentation of ES disease, then a PET scan is not needed because it will not add any useful staging information. At present, data are insufficient to make recommendations regarding the potential role of PET scans in restaging, response evaluation, or prognostic predictions in patients with SCLC. There are no reports to suggest that a bone scan adds useful staging information if a PET scan has already been obtained.

2.4 Recommendations

2.4.1. 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 of the chest and abdomen with intravenous contrast or CT scan of the chest extending through the liver and adrenal glands, MRI or CT of the brain, and bone scan (Grade 1B)**.**

2.4.2. In patients with clinically limited-stage (LS)-SCLC, PET imaging is suggested (Grade 2C)**.**

Remark: If PET is obtained, then bone scan may be omitted.

2.4.3. In patients with SCLC, it is recommended that both the Veterans Administration system (LS vs extensive stage [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)**.**

3.0 Role of Surgery

A prospective randomized trial comparing surgery and radiotherapy in the 1960s and two subsequent meta-analyses demonstrating the benefits of radiotherapy led to the initial abandonment of surgery in the treatment of SCLC.[38-40] After analyzing two randomized and eight nonrandomized comparative observational studies, the second edition of the ACCP Lung Cancer Guidelines found inadequate objective evidence to categorically support any recommendation regarding surgery for SCLC, although the authors "favored" surgery in select patients with clinical stage I SCLC after aggressive mediastinal and systemic staging.[41] Adjuvant chemotherapy has not been evaluated in prospective randomized trials. However, several reports have suggested a benefit of chemotherapy after complete surgical resection, leading to a level 2C recommendation in the second edition of the ACCP guidelines.[42-50]

The role of surgery in SCLC has been analyzed recently using two large population databases. A study of data from 1988 to 2002 in the US SEER database identified 14,179 patients with SCLC, including 863 (6.1%) who underwent surgery.[49] Surgery was more commonly done for patients with T1/T2 disease ($P < .001$). Patients undergoing surgery had better survival than those not undergoing surgery for both localized and regional disease, with median survivals of 42 months vs 15 months ($P < .001$) and 22 months vs 12 months ($P < .001$), respectively. After surgery, the 5-year overall survival rates were 45% for localized disease and 26% for regional disease. Patients with N2 disease were the only subset that benefited from postoperative radiation therapy (RT) ($P = .01$). Another comparative study from 1988 to 2004 using the SEER database analyzed patients treated for stage I SCLC.[51] Patients who did not undergo surgical therapy (n = 1161) were compared with patients who underwent lobectomy (n = 247, 15.8%), with 15% of patients receiving postoperative RT. The routine administration of adjuvant systemic therapy was assumed, but data were not available for confirmation. The 5-year overall survival in patients undergoing lobectomy was 50% without and 57% with postoperative radiation ($P = .9$). In contrast, a 5-year overall survival was 15% in patients treated with external beam RT alone. Finally, the IASLC reported on 12,620 patients with SCLC, of whom 349 (2.8%) underwent surgical therapy.[10] Prognosis was analyzed using the seventh edition TNM staging for lung cancer. Survival after resection correlated with both the T and N categories, with nodal status having a stronger influence on survival. Overall 5-year survival for pathologic stage IA disease was 53%, with T1 and N0 tumors demonstrating 45% and 49% 5-year survival, respectively. This study also analyzed concordance between the clinical and pathologic stages. Twenty percent of patients who were clinically stage I/II were upstaged with pathologic evidence of mediastinal lymph node metastases. The disparity in clinical and pathologic mediastinal staging has also been reported in a small prospective Japanese trial.[52] Although modern-day FDG-PET imaging may improve clinical staging, these data stress the importance of aggressive mediastinal staging prior to considering surgical therapy.

Although <5% of patients with SCLC present with stage I disease, the increasing use of CT scanning and minimally invasive surgery to remove suspicious lung nodules without prior biopsy may increase this percentage in the future. Recent reports analyzing large population databases continue to support surgery in select patients with clinical stage I SCLC after aggressive systemic and mediastinal staging. These studies suggest a role for surgery in SCLC; however, because of their retrospective design, it is impossible to correct

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for possible confounding by selection of patients with a better prognosis for surgery. Furthermore, many series of patients with SCLC who received surgical resection have reported that approximately one-half of the patients were not suspected of having SCLC prior to resection. Adjuvant systemic therapy is also recommended for all stages of SCLC following complete resection.

3.1 Recommendations

3.1.1. 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) is recommended (Grade 1B)**.**

3.1.2. In patients with clinical stage I SCLC after a thorough distant and invasive mediastinal stage evaluation, surgical resection is suggested over non-surgical treatment (Grade 2C)**.**

3.1.3. In patients with stage I SCLC who have undergone curative-intent surgical resection, platinum-based adjuvant chemotherapy is recommended (Grade 2C)**.**

4.0 Use of RT for SCLC

The use of RT for SCLC can be thought of in terms of TRT, prophylactic cranial irradiation (PCI), and RT used for the palliation of various metastases. RT has long been established as an effective palliative therapy for metastases and thus will not be reviewed here (see the symptom management article of the lung cancer guidelines[53]).

4.1 The Role of TRT in SCLC

The Veterans Administration Hospital System performed a phase 3 trial for patients with unresectable lung cancer (including both SCLC and non-SCLC).[54] Five hundred fifty-four patients with localized but clinically inoperable bronchogenic carcinoma were randomized to receive TRT (n = 308) or an inert compound (n = 240). The median survival of patients given TRT was 142 days, compared with 112 days ($P = .05$) for those who received the inert compound. However, TRT had no apparent effect in prolonging the lives of patients with anaplastic small cell carcinoma. Thus, by itself, TRT did not appear to influence the survival of patients with LS-SCLC.

The use of TRT was reexamined after the use of chemotherapy became widespread in this disease. In 1992, two meta-analyses regarding the role of TRT in addition to chemotherapy in LS-SCLC were published. Pignon et al[39] analyzed 13 phase 3 trials that compared chemotherapy alone to chemotherapy + TRT and reported that the 3-year survival rate was 14.3% with chemotherapy + TRT and 8.9% with chemotherapy alone ($P = .001$). Warde and Payne[40] analyzed 11 phase 3 trials and reported a similar 5.4% improvement in 2-year survival for patients receiving chemotherapy + TRT ($P < .001$). Although this 5.4% improvement appears rather small, it represented a 61% increase in the 3-year survival of 8.9% achieved with chemotherapy alone. Local failure was noted in 52% of patients who received chemotherapy + TRT and 77% of those who received chemotherapy alone ($P < .0001$). Since the publication of these meta-analyses, chemotherapy + TRT has become the standard of care for patients with LS-SCLC.

Additionally, much work has been done to determine the optimal timing of TRT administration. In 2004, Fried et al[55] published a meta-analysis evaluating seven randomized trials addressing the timing of TRT relative to chemotherapy in LS-SCLC.[55] Early TRT was designated as that initiated < 9 weeks after starting chemotherapy and late TRT ≥ 9 weeks after chemotherapy. The relative risk of survival for early TRT vs late TRT was 1.17 ($P = .03$), indicating an increased survival for early TRT. This translated into a 5.2% ($P = .03$) increase in the 2-year survival of patients receiving early TRT. This small improvement in 2-year survival for early TRT was similar in overall magnitude to the benefit of adding TRT to chemotherapy. Thus, the timing of TRT appears to be an important variable to consider in optimizing therapy.

De Ruysscher et al[56] performed a subsequent meta-analysis that also focused on the timing of TRT. Eight phase 3 trials comparing two different radiation schedules, with the same chemotherapy regimen in both arms, were included. The interval between the start of any treatment and the end of TRT (SER) was found to be the most important predictor of outcome, with a higher 5-year survival rate in the shorter SER arms. A low SER was also associated with a higher risk of severe esophagitis. Each week of extension of the SER beyond that of the arm with the shortest SER resulted in an overall absolute decrease in the 5-year survival rate of $1.83\% \pm 0.18\%$ (95% CI). Thus, it appears best to administer TRT both early and within a short time period.

Regarding the dose of TRT, there are data supporting the use of higher biologically effective dose (BED) regimens. The BED is a mathematical construct used to estimate the relative kill power of a particular RT regimen. The formula for the BED can be extended to include parameters of time. Higher-dose regimens administered in fewer fractions have higher BED values and result in greater tumor cell kill, but can also result in greater toxicity.

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Turrisi et al[57] (Eastern Cooperative Oncology Group [ECOG] 3588/Intergroup Trial 0096) reported the results of a phase 3 trial that included 417 patients with LS-SCLC. All the patients received four cycles of etoposide plus cisplatin (EP). Patients were randomly assigned to receive a total of 45 Gy of concurrent TRT, either bid in 1.5-Gy fractions over a 3-week period or once daily in 1.8-Gy fractions over a period of 5 weeks. The TRT began on day 1 of chemotherapy in both arms. The 5-year survival rates were 16% for once daily TRT vs 26% for bid-TRT. The median survival was 19 months for once daily TRT and 23 months for bid-TRT ($P = .04$). The local failure rate was 26% for bid-TRT and 52% for once daily TRT ($P = .06$). There was a higher rate of grade 3 esophagitis with the bid-TRT (27%) than with the once daily TRT (11%) ($P < .001$).

The North Central Cancer Treatment Group (NCCTG) performed a trial (89-20-52) that has been misinterpreted as contradicting the findings of Intergroup Trial 0096. The findings of these studies provide complimentary information regarding bid-TRT. This NCCTG trial included 310 patients with LS-SCLC initially treated with three cycles of EP.[58] Subsequently, the 261 patients without progression were randomized to two cycles of EP plus either once daily-TRT (50.4 Gy/28 fractions) or split-course bid-TRT (24 Gy/16 fractions followed by a 2.5-week break and then an additional 24 Gy/16 fractions). Patients then received a sixth cycle of EP followed by PCI. The median survival and 5-year survival rate from randomization were 20.6 months and 21% for patients who received once daily-TRT and 20.6 months and 22% for those who received bid-TRT ($P = .68$). Esophagitis of $>$ grade 3 ($P = .05$) was more common in the bid arm, as was treatment-related death, which occurred in four of 130 patients (3%) who received bid-TRT and zero of 131 (0%) who received once daily-TRT ($P = .04$). The findings of these two randomized prospective studies comparing once daily- and bid-TRT for LS- SCLC led to the conclusion that continuous-course bid-TRT is better than once daily-TRT, but split-course bid-TRT is not. This finding is identical to the findings regarding bid-RT in head and neck cancer. The Radiation Therapy Oncology Group conducted a phase 3 randomized trial (RTOG 9003) in patients with locally advanced squamous cell carcinomas of the head and neck that compared various radiotherapy regimens. Patients treated in the continuously administered bid-RT arms had better local regional control than those treated with split-course bid or standard once daily RT arms. This study also found that although continuously administered bid-RT was better than once daily RT, split-course bid-RT was not.[59]

Le Pechoux et al[60] presented a meta-analysis of radiotherapy in LS-SCLC based on individual patient data from trials on hyperfractionated and/or accelerated radiotherapy. This study compiled the data from the ECOG 3588/Intergroup Trial 0096 and NCCTG 89-20-52. The combined data revealed a 5% survival advantage at 5 years for the bid-TRT approach over the once daily TRT approach ($P = .08$). Again, it appears that the inclusion of the split-course bid-TRT cohort in NCCTG 89-20-52 diluted the findings to some degree because the split-course regimen increased the overall time during which the TRT was administered and probably allowed for some degree of tumor repopulation to have occurred, which negatively influenced patient survival.

Schild et al[61] provided further data suggesting a correlation between patient survival and the BED of TRT. Data from 904 patients in eight trials evaluating EP chemotherapy and various TRT regimens were combined. The BED of the TRT was plotted against the 5-year survival rates reported in these studies. The Pearson correlation coefficient between the BED and 5-year survival was 0.81, indicating a strong positive correlation.

Although the role of TRT is less clear in patients with ES-SCLC, there may be a distinct survival benefit to delivering the TRT as part of the initial management of carefully selected patients. Jeremic et al[62] reported the results of a randomized prospective study that evaluated chemotherapy with or without bid-TRT in patients with ES-SCLC. Patients initially received three cycles of carboplatin and etoposide. Those patients with a CR at distant sites and a partial response or better in the chest were randomly assigned to receive either bid-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 [MST] 17 months vs 11 months and 5-year survival rate 9.1% vs 3.7%; $P = .041$). This study revealed the positive influence of a relatively aggressive course of TRT on the survival of carefully selected patients with ES-SCLC. It appears that the patients who benefit are those in whom the RT encompasses all known radiographically detectable residual disease in the body.

The evidence (Level: 1A) strongly supports the therapeutic value, in terms of improved survival, of concurrent chemotherapy and TRT for patients with LS-SCLC. The available data also suggest that TRT should begin early and be completed quickly; the TRT fractionation programs that satisfy these parameters have been associated with better survival. Patients with ES-SCLC who have a CR of all disease outside of the chest also appear to benefit from TRT.

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4.2 Prophylactic Cranial Irradiation

PCI was first tested for patients with SCLC in the 1970s following the recognition that brain metastases occurred frequently despite excellent systemic responses to chemotherapy. The blood-brain barrier prevents the penetration of most chemotherapeutic agents, leaving the brain as a sanctuary site for relapse. The first trials demonstrated a substantial reduction in the incidence of brain metastases.[63] Unfortunately, a number of long-term survivors of SCLC who had undergone PCI were noted to have various neurologic abnormalities, including dementia.[64,65] MRI findings were described as "leukoencephalopathy" because of changes within the white matter consistent with demyelination. These findings were especially frequent when PCI was delivered in large daily doses (such as 3.6-Gy daily fractions × 10 for a total of 36 Gy) or concurrently with chemotherapy.[66] These reports of leukoencephalopathy contributed to a subsequent lack of enthusiasm for PCI. Despite these hesitations, careful prospective studies revealed that PCI improved survival for both ES-SCLC and LS-SCLC and was reasonably safe when administered sequentially after chemotherapy using less-toxic dose-fractionation regimens.

In addition to TRT, PCI has been shown to positively influence survival in patients with LS-SCLC and ES-SCLC who achieve a CR. Aupérin et al[67] published a meta-analysis that included data from seven randomized prospective studies that compared PCI with no PCI after a CR was achieved. The 3-year survival rate was 5.4% better for those who received PCI (20.7% vs 15.3%, $P = .01$). Although 5.4% appears small, it does reflect a 35% increase in 3-year survivors. A statistically significant PCI dose-response was noted for the risk of brain recurrence, but not survival. Neurotoxicity was not evaluated in this analysis.

More recently, Patel et al[68] provided supporting data that PCI was associated with the survival of patients with LS-SCLC. This large retrospective analysis included 7,995 patients with LS-SCLC from the SEER database. The 5-year survival was 11% without PCI and 19% with PCI ($P < .001$). On multivariate analysis, age, sex, extent of primary disease, size of disease, extent of lymph node involvement, and PCI were found to be significant predictors of survival ($P < .001$). The authors concluded that PCI is indicated for patients with LS-SCLC.

The role of PCI was also verified to be important for the majority of patients with ES-SCLC. Slotman et al[69] conducted a randomized trial (European Organization for Research and Treatment of Cancer 08993-22993) of PCI in patients with ES-SCLC who had had any degree of response to chemotherapy. Patients were randomly assigned to undergo PCI or to receive no further therapy. The primary end point was the time to symptomatic brain metastases. CT scanning or MRI of the brain was performed when any predefined key symptom suggestive of brain metastases was present, but was not done routinely prior to PCI. The two groups (each with 143 patients) were well balanced regarding baseline characteristics. 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 [HR], 0.27; $P < .001$). PCI was associated with an increase in median overall survival from 5.4 to 6.7 months after randomization. The 1-year survival rate was 27.1% in the PCI group and 13.3% in the control group ($P = .003$). PCI had side effects but did not have a clinically significant effect on global health status. The largest mean difference between the two arms was observed in fatigue and hair loss, which were greater in those who received PCI.[70] PCI reduced the incidence of symptomatic brain metastases and prolonged overall survival in patients with ES-SCLC.[69]

The European Organization for Research and Treatment of Cancer also evaluated dose-fractionation patterns for PCI in an international phase 3 trial.[71] This randomized trial compared the effect of standard vs higher PCI doses on the incidence of brain metastases in 720 patients with LS-SCLC in complete remission after chemotherapy and TRT. Patients were randomly assigned to a standard PCI dose (n = 360, 25 Gy in 10 daily fractions of 2.5 Gy) or a higher PCI total dose (n = 360, 36 Gy) delivered using either conventional fractionation (18 daily fractions of 2 Gy) or accelerated hyperfractionation (24 fractions in 16 days with two daily sessions of 1.5 Gy). The primary end point was the incidence of brain metastases at 2 years. There was no significant difference in the 2-year incidence of brain metastases between the standard PCI dose group and the higher-dose group (29% vs 23%; $P = .18$). The 2-year overall survival was 42% in the standard-dose group and 37% in the higher-dose group ($P = .05$). The most common acute toxic events were fatigue (30% of patients in the standard-dose group vs 34% in the higher-dose group), headache (24% vs 28%), and nausea or vomiting (23% vs 28%). There was a nonsignificant reduction in the total incidence of brain metastases observed after higher-dose PCI and there was also a significant increase in mortality. Therefore, PCI at 25 Gy in 10 fractions should remain the standard dose-fractionation pattern used in SCLC.[71]

Based on the currently available evidence, it is recommended that patients with SCLC achieving a complete or partial response to initial therapy should be offered PCI, because it significantly improves survival. The current standard dose-fractionation pattern is 25 Gy/10 fractions.[71] Although data are lacking

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regarding the optimal timing of PCI, it is likely best given after all planned chemotherapy has been administered.

4.3 Recommendations

4.3.1. In patients with LS-SCLC, early chemoradiotherapy, with accelerated hyper-fractionated radiation therapy (twice-daily treatment) concurrently with platinum-based chemotherapy, is recommended (Grade 1B)**.**

4.3.2. In patients with LS- or ES-SCLC who achieve a complete or partial response to initial therapy, PCI is recommended (Grade 1B)**.**

Remark: The regimen of 25 Gy in 10 daily fractions has the greatest supporting data for safety and efficacy.

4.3.3. In patients with ES-SCLC who have completed chemotherapy and achieved a CR outside the chest and complete or partial response in the chest, a course of consolidative TRT is suggested (Grade 2C)**.**

5.0 Use of Chemotherapy for SCLC

Two randomized phase 3 trials evaluated doxorubicin-based chemotherapy compared with platinum-based chemotherapy in SCLC. Baka and associates[72] enrolled patients with either LS- or ES-SCLC who were randomized to either doxorubicin, cyclophosphamide, and etoposide (ACE) or EP for six cycles. There were no differences in response rates (72% vs 77%) or MST for LS (10.9 months vs 12.6 months) or ES (8.3 months vs 7.5 months). More grade 3/4 neutropenia and infections occurred on the ACE regimen. A study from the Netherlands compared ACE with paclitaxel and carboplatin for five cycles in ES-SCLC. The response rates and progression-free survival were similar, but grade 4 leukocytopenia (64% vs 9%) and febrile neutropenia (30% vs 4%) were substantially greater with ACE therapy ($P < .0001$).[73] A Cochrane systematic review of platinum vs non-platinum chemotherapy regimens evaluated 29 trials with 5,530 patients and concluded that platinum-based chemotherapy regimens did not offer a statistically significant benefit in either overall tumor response or survival.[74] The review noted a lack of quality-of-life data in trials with chemotherapy for SCLC and recommended this be addressed in future trials. In practice, platinum-based chemotherapy regimens have replaced alkylator- and anthracycline-based regimens in patients with both LS- and ES-SCLC because of its more favorable toxicity profile and the ability to administer full-dose chemotherapy along with definitive radiation.

In 2002, a study by Japanese investigators reported that irinotecan and cisplatin (IP) resulted in a substantial improvement in survival compared with treatment with EP (median survival 420 days vs 300 days).[75] Since 2004, multiple randomized phase 3 trials, a systematic review, and one meta-analysis have compared treatment with EP with platinum and a topoisomerase inhibitor (Fig 3)[76-82] using various doses, schedules, or preparations (po vs IV). The Southwest Oncology Group conducted a randomized prospective study in North America with 651 patients randomized to IP or EP.[82] The dose and schedule of the drugs were identical to those employed by Noda et al[75] in the Japanese trial. The MSTs were identical (9.9 months vs 9.1 months) for IP vs EP ($P = .71$). Severe diarrhea was more common with IP (19% vs 3%), whereas severe neutropenia (68% vs 33%) and thrombocytopenia (15% vs 4%) were greater with EP. The North American trial failed to confirm the previously reported benefit in survival with IP that was reported in the Japanese trial. Lara and colleagues[77] performed a common arm comparative outcomes analysis between the North American and the Japanese trials and noted significant differences in patient demographics, toxicity, and efficacy in the two populations. Differences in ethnic pharmacogenomics may have accounted for the variation in response and toxicity and should be incorporated into future trials with ethnic/national differences. In general, the phase 3 trials have shown equivalent efficacy with EP and IP with variation in their toxicity profile as noted above.

A meta-analysis of camptothecins compared with etoposide in combination with platinum analogs used reported data (not individualized patient data) from eight trials and demonstrated a statistically significant benefit with IP over EP regimens in both PFS and overall survival (HR, 0.87; 95% CI, 0.78-0.97; $P = .02$).[83] IP caused more diarrhea, but less hematologic toxicities. The National Comprehensive Cancer Network guidelines on ES-SCLC recommends treatment with two drug regimens of either cisplatin or carboplatin plus etoposide or irinotecan.[84]

The addition of a third drug to a platinum regimen was reviewed in the second edition of the ACCP guidelines and was shown to add to toxicity, but not to improve overall survival.[41] Accordingly, the ACCP guidelines, as well as the National Comprehensive Cancer Network guidelines, have uniformly advised against a three-drug regimen and have recommended platinum-based, doublet chemotherapy. Two drugs that have been further evaluated since the last guideline are paclitaxel and pemetrexed. de Jong et al[73] compared cisplatin and paclitaxel with ACE and observed response rates of 61% and 60%, respectively, and PFS of 5.2 months and 4.9 months, respectively, ($P = .60$). The cisplatin/paclitaxel regimen had significantly less toxicity.

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FIGURE 3. Etoposide and cisplatin compared with platinum and a topoisomerase inhibitor.

Trial	Phase	No.	Tmt Arms		RR (%)		Survival				Toxicity (grade 3,4)	
							MST (mo)		% 1-y		% 2-y			
			Cntr	Exp	Cntr	Exp	Cntr	Exp	Cntr	Exp	Cntr	Exp	Cntr	Exp
Eckardt[76, a]	III	784	EP	TP	69	63	10	9.8	31	31	--	--	↑ neutropenia	↑ anemia; thrombocytopenia
Lara[82, b]	III	651	EP	IP	57	60	9.1	9.9	34	41	--	--	↑ neutropenia, thrombocytopenia	↑ diarrhea
Zatloukal[78, c]	III	405	EP	IP	47	39	9.7	10.2	39	42	8	16	↑ neutropenia	↑ diarrhea, vomiting
Hanna[79, d]	III	331	EP	IP	44	48	10.2	9.3	35	35	8	8	↑ neutropenia, anemia, thrombocytopenia	↑ dehydration, diarrhea, vomiting
Schmittel[80, e]	III	216	EC	IC	52	54	9	10	30	37	--	--	↑ hematologic toxicity	↑ diarrhea
Hermes[81, f]	III	209	EC	IC	--	--	7.1	8.5	24	34	--	--	↑ thrombocytopenia	↑ diarrhea

AUC = area under the curve; C = control; E = experimental; MST = median survival time, Tmt = treatment. See Figure 1 for expansion of other abbreviations.

[a]EP (etoposide 100 mg/m²/d × 3, cisplatin 80 mg/m²/d1) vs oral TP (topotecan 1.7 mg/m²/d × 5, cisplatin 60 mg/m²/d5).

[b]EP (etoposide 100 mg/m²/d1-3, cisplatin 80 mg/m²/d1) vs IP (irinotecan 60 mg/m²/d1,8,15, cisplatin 80 mg/m²/d1).

[c]EP (etoposide 100 mg/m²/d1-3, cisplatin 80 mg/m²/d1) vs IP (irinotecan 65 mg/m²/d1 + 8, cisplatin 80 mg/m²/d1).

[d]EP (etoposide 120 mg/m²/d1-3, cisplatin 60 mg/m²/d1) vs IP (irinotecan 65 mg/m²/d1 + 8, cisplatin 30 mg/m²/d1 + 8).

[e]EC (etoposide 140 mg/m²/d1-3, carboplatin AUC 5) vs IC (irinotecan 50 mg/m²/d1,8,15, carboplatin 80 AUC 5).

[f]EC (etoposide 120 mg/m²/d1-5 po, carboplatin AUC 4/d1) vs IC (irinotecan 175 mg/m²/d1, carboplatin AUC 4/d1).

A Hellenic group randomized 108 patients with LS or ES disease to paclitaxel/cisplatin or EP.[85] The response rates were similar, and the MSTs were 12 and 13 months, respectively ($P = .354$). The paclitaxel regimen was not superior to EP. A phase 3 trial by the Cancer and Leukemia Group B randomized 578 patients with ES disease to treatment with EP without or with paclitaxel (TEP) and granulocyte colony-stimulating factor.[86] The median failure-free survival time was 5.9 months (EP) vs 6 months (TEP) and the MST was 9.9 months (EP) vs 10.6 months (TEP). Treatment-related deaths were 2.4% on the EP regimen vs 6.5% with TEP. The authors concluded that TEP did not improve the time to progression or survival and was associated with excessive toxicity.

The chemotherapy doublet of pemetrexed and cisplatin or carboplatin has demonstrated activity in malignant pleural mesothelioma and nonsquamous lung cancer. An initial phase 2 study of pemetrexed and cisplatin or carboplatin yielded promising results.[87] A phase 3 trial in patients with ES disease compared pemetrexed/carboplatin with etoposide/carboplatin.[88] Accrual was terminated early by the data safety monitoring committee with 908 of 1,820 planned patients enrolled. The pemetrexed/carboplatin arm was inferior for both progression-free survival (3.8 months vs 5.4 months) and overall survival (median 8.1 months vs 10.6 months) (HR, 1.56; 95% CI, 1.27-1.92; $P < .01$). Pemetrexed with either carboplatin or cisplatin is no longer used in SCLC.

In summary, EP has been shown to have efficacy equivalent to alkylator-based regimens with a more favorable toxicity profile. Several other platinum-based regimens, particularly platinum plus irinotecan, have been evaluated in phase 2 and 3 trials, but none have proven superior to EP or EC, and they frequently carry added toxicity. Many other strategies, including maintenance therapy, alternating regimens, triplet therapy, dose-intense regimens, and dose-dense chemotherapy, have failed to demonstrate consistent benefits, and many of these approaches have led to unacceptable toxicity. Therefore, EP and EC remain the standard chemotherapy regimens for patients with both LS- and ES-SCLC.

6.0 Novel Therapies

Thalidomide, believed to be an antiangiogenic agent, was tested in two trials. In a trial from the United Kingdom, 724 patients with LS (51%) or ES (49%) were randomized to thalidomide, 100 to 200 mg daily for 2 years, or placebo.[89] All patients received etoposide and carboplatin every 3 weeks for six cycles. The median overall survival was 10.5 months (placebo) and 10.1 months (thalidomide) with an HR of 1.09 (95% CI, 0.93-1.27; $P = .28$). Among patients with LS disease

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there was no difference in survival; however, those patients with ES who were treated with thalidomide had a worse survival. Thalidomide was associated with an increased risk of thrombotic events, mainly DVT and pulmonary embolism. French investigators evaluated thalidomide, 400 mg daily, or placebo as maintenance therapy in patients with ES-SCLC who had responded to treatment after two cycles of a four-drug regimen of etoposide, cisplatin, cyclophosphamide, and epidoxorubicin.[90] Ninety-two patients were randomized (49 to thalidomide). Survival was not significantly better with thalidomide and neuropathy was more frequent in the thalidomide group.

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor. It is approved for the treatment of non-SCLC. Three nonrandomized phase 2 trials have combined bevacizumab with EP, IP, and irinotecan and carboplatin. The response rates were 64% to 84% with MSTs of 10.9, 11.7, and 12.1 months, respectively.[91-93] Phase 3 trials are currently in progress, but at this time bevacizumab is not recommended for the treatment of SCLC outside a clinical trial setting. Other antiangiogenic agents are under evaluation, but none have been shown to be beneficial in a phase 3 trial. Although many targeted therapy agents have been evaluated in SCLC, none has demonstrated clinical benefit.

6.1 Recommendation

6.1.1. 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 is recommended over other chemotherapy regimens (Grade 1A)**.**

7.0 Second-line Treatment of SCLC

Most patients who present with LS-SCLC and nearly all with ES-SCLC will develop recurrent disease. Patients with recurrent SCLC can be divided into two categories based on the likelihood of response to second-line therapy: refractory/resistant disease (primary progression or recurrence within 3 months of initial therapy) or relapsed/sensitive disease (recurrence >3 months after initial therapy). Patients with refractory/resistant disease exhibit much lower response rates with second-line therapy. Of the 12 randomized trials that evaluated the management of patients with recurrent SCLC, five assessed chemotherapy regimens or concepts that are no longer relevant to modern clinical care and therefore these are not discussed further.[94-98]

In light of the relatively short survival of patients with recurrent SCLC, even in those receiving subsequent chemotherapy, it is reasonable to ask whether further therapy provides any benefit. Only one randomized trial has sought to clearly answer this question. O'Brien et al[99] randomized 141 patients who were not considered candidates for further IV chemotherapy to receive either oral topotecan or best supportive care. Although the response rate to oral topotecan was only 7%, overall survival was significantly better in patients receiving chemotherapy (MST, 26 weeks vs 14 weeks; 6-month survival, 49% vs 26%; $P = .01$) (Fig 4).[99-105] In addition, patients in the topotecan arm had a slower decline in quality of life than did those not receiving chemotherapy.[99]

Many small, single-arm trials of single agents and combination regimens have been performed in patients with relapsed SCLC. Single agents with demonstrated activity in the second-line setting include topotecan, irinotecan, paclitaxel, docetaxel, vinorelbine, oral etoposide, and gemcitabine. Although response rates are generally higher with combination therapy, overall survival does not appear to be improved and the toxicity of combination regimens is frequently problematic. Only one randomized trial has directly compared single-agent therapy with a combination regimen in patients with recurrent SCLC. von Pawel et al[100] randomized 211 patients with SCLC who had relapsed >60 days after initial therapy to receive either single-agent topotecan or the combination of cyclophosphamide, doxorubicin, and vincristine (CAV). There were no significant differences in response rates (24% vs 18%, $P = .29$), time to progression (13 weeks vs 12 weeks, $P = .55$), or overall survival (median, 25 weeks vs 25 weeks, $P = .79$) between patients treated with topotecan or CAV (Fig 4).[100] However, hematologic toxicity was significantly greater with the combination therapy. Based on these results, single-agent chemotherapy is recommended as the standard second-line treatment approach for patients with SCLC.

Two randomized studies have compared oral and IV topotecan in patients with recurrent SCLC.[101,102] Although these studies were designed for patients with relapsed/sensitive disease, a small number of patients with refractory/resistant disease were also enrolled. Overall, there were no statistically significant or clinically meaningful differences in response rate, progression-free survival, or overall survival noted between patients receiving oral or IV topotecan (Fig 4).[101] Quality-of-life assessment was also similar with oral and IV topotecan,[102] although the oral formulation was associated with less severe neutropenia.[101,102]

Recent studies have demonstrated that amrubicin, an investigational anthracycline, has promising activity in patients with SCLC. Three randomized trials have compared amrubicin with topotecan as second-line therapy. A randomized phase 2 trial from Japan compared amrubicin with topotecan in 59 patients with recurrent SCLC and reported significant improvements

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FIGURE 4. Randomized trials in relapsed small cell lung cancer.

Trial	Phase	N	% Resis-tant	Days from 1st Tmt	Tmt Arms		RR (%)		Survival					Toxicity (grade 3,4)	
									MST (mo)		% 1-yr		p		
					Cntr	Exp	Cntr	Exp	Cntr	Exp	Cntr	Exp		Contr	Exp
BSC vs. Single-agent															
O'Brien[99, a]	III	141	54	> 45	BSC	T	--	7	3.5	6.5	26[a]	49[a]	0.01	--	slower ↓QOL TRD 6%
Single-agent vs Combination chemotherapy regimen															
Von Pawel[100, c]	III	211	20	> 60	CAV	T	18	24	6.2	6.2	14	14	NS	> ↓ ANC, TRD 4%	↓ symptoms; > ↓ plt, TRD 6%
IV vs. Oral Topotecan															
Von Pawel[101, d]	II	106	2	> 90	T *IV*	T *po*	15	23	6.3	8	-	-		> ↓ ANC, TRD 0	TRD 2%
Eckardt [102, e]	III	304	9	> 90	T *IV*	T *po*	22	18	8.8	8.3	29	33	NS	> ↓ ANC, TRD 3%	> ↓ plt, TRD 4%, similar QOL
Topotecan vs. Amrubicin															
Inoue [103, f]	II	59	40		T *IV*	Am	13	38	8.4	8.1	-	-		>↓ ANC, >non-heme tox, TRD 3%	TRD 0%
Jotte [104, g]	II	76	0	> 90	T *IV*	Am	15	44	7.6	9.2	33	36		↑ heme tox, TRD 13%	TRD 10%
Jotte [105, h]	III	637	46	> 90	T *IV*	Am	17	31	7.8	7.5	25	28		↑ heme tox	↑ FN/Infection

Am = amrubicin; ANC = absolute neutrophil count; BSC = best supportive care; CAV = cyclophosphamide + doxorubicin + vincristine; FN = febrile neutropenia; heme = hematologic; NS = not significant; plt = platelet count; QOL = quality of life; RR = response rate, T = topotecan; tox = toxicity; TRD = treatment-related deaths. See Figure 3 for expansion of other abbreviations.

[a]BSC vs topotecan po 2.3 mg/m²/d ×5 d.

[b]6-mo data.

[c]CAV vs topotecan IV 1.5 mg/m²/d × 5 d.

[d]Topotecan IV 1.5 mg/m²/d × 5 d vs topotecan po 2.3 mg/m²/d × 5 d.

[e]Topotecan IV 1.5 mg/m²/d × 5 d vs topotecan po 2.3 mg/m²/d × 5 d.

[f]Topotecan IV 1.0 mg/m²/d × 5 d vs amrubicin 40 mg/m²/d × 3 d.

[g]Topotecan IV 1.5 mg/m²/d × 5 d vs amrubicin 40 mg/m²/d × 3 d.

[h]Topotecan IV 1.5 mg/m²/d × 5 d vs amrubicin 40 mg/m²/d × 3 d.

in response rate (38% vs 13%, $P = .04$) and disease control rate (79% vs 46%, $P = .02$) in patients receiving amrubicin (Fig 4).[103] Response rates for amrubicin and topotecan were 53% and 21%, respectively, in patients with relapsed/sensitive disease and 17% and 0%, respectively, in patients with refractory/resistant disease. Similarly, a randomized phase 2 trial from the United States that compared amrubicin with topotecan in 76 patients with relapsed/sensitive SCLC demonstrated a significant improvement in response rate (44% vs 15%, $P = .02$) with amrubicin (Fig 4).[104] Jotte et al[105] recently reported a phase 3 trial in which 637 patients with recurrent SCLC were randomized in a 2:1 manner to receive either amrubicin or topotecan. There was a significant improvement in response rate (31% vs 17%, $P = .0002$) with amrubicin, but no significant difference in median progression-free survival (4.1 months vs 4.0 months, $P = .98$) or overall survival (7.5 months vs 7.8 months, $P = .17$) (Fig 4).[105] Interestingly, in the subgroup of patients with refractory/resistant disease, the 1-year overall survival rate was significantly better with amrubicin (17% vs 8%, $P = .019$). Although topotecan resulted in significantly more severe myelosuppression, amrubicin led to a significantly greater rate of febrile neutropenia and infections. Overall, in patients with recurrent SCLC, amrubicin results in higher response rates than does topotecan, particularly for those with resistant/refractory disease; however, survival is poor in these patients and despite better response, overall survival does not appear to be improved.[105]

Several older, nonrandomized trials reported that for patients with sensitive relapse, particularly those with a longer initial response duration, retreatment with the initial chemotherapy regimen resulted in response rates of 50% to 60%.[106,107] Based on these findings, retreatment with the initial chemotherapy regimen has been recommended for patients relapsing ≥ 6 months from initial therapy.

7.1 Recommendation

7.1.1. 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 relapse > 6 months from completion of initial chemotherapy. Enrollment in a clinical trial is encouraged.

8.0 Treatment of SCLC in the Elderly

The definition of "elderly" varies throughout the oncology literature, but most studies, including the majority of those dealing with lung cancer, define elderly as 70 years of age or older. Among patients diagnosed with SCLC, about 43% are ≥ 70 years old and 10% are ≥ 80 years old.[108] Unfortunately, despite the frequent occurrence of SCLC in the elderly, the enrollment of elderly patients in clinical trials is low, and few high-quality, randomized trials have specifically focused on the treatment of SCLC in this patient population. In addition, many trials have combined elderly patients and those with a poor performance status (PS) without reporting outcomes separately for the two groups, making it difficult to determine the appropriate therapeutic conclusion for these distinct populations.

The primary question that has been asked in clinical trials in elderly patients with SCLC is whether lower-intensity regimens can yield equivalent outcomes with less toxicity than standard-treatment regimens. In the only randomized trial that exclusively enrolled elderly patients, Ardizzoni et al[109] compared a standard regimen of EP with a reduced-dose EP regimen in 95 patients ≥ 70 years old with an ECOG PS of 0 to 2. Although the reduced-dose EP regimen did result in marginally less severe toxicity, it also led to lower response and overall survival rates (Fig 5).[109-111] Two other randomized trials have included both elderly patients and patients with a poor PS. Okamoto et al[110] compared an EP regimen to the combination of carboplatin and etoposide in 220 patients with ES-SCLC. Ninety-two percent of patients were ≥ 70 years old with a PS of 0 to 1, and only 8% were < 70 years old with a PS of 3. There were no significant differences in response rate, progression-free survival (PFS), or overall survival between the two arms in the overall study population or in the subgroup of patients ≥ 70 years old with a good PS (Fig 5). Souhami et al[111] compared a regimen of EP alternating to CAV with single-agent oral etoposide in 155 patients who were either ≥ 75 years old with any PS or < 75 years old with a PS of 2 to 3.[111] All relevant efficacy end points, including response rate, PFS, overall survival, and quality-of-life score, were significantly worse in patients who received single-agent etoposide (Fig 5). However, there was no information provided on how many patients enrolled in this trial were elderly or had a poor PS, and there were no separate data analyses for these distinct populations.

Several large clinical trials of patients with SCLC have been analyzed retrospectively to evaluate the effect of age on outcome. Yuen et al[112] reported a retrospective age analysis of INT-0096, in which 381 patients with LS-SCLC and a PS of 0 to 2 were randomized to receive standard EP with either once-daily or bid radiotherapy. In this study, only 13% of patients were ≥ 70 years old and 3% were ≥ 75 years old. Although response rates and PFS were similar in

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FIGURE 5. Randomized trials in elderly patients with small cell lung cancer.

Trial, Year	Phase	N (%LD)	Median Age (range)	Chemotherapy Treatment Arms	Response OR/SD	Median PFS (mo)	Overall Survival		Toxicity
							MST (mo)	% 1-year	
Ardizzoni 2005[109]	II	28 (57%)	74 (70-80)	P 25 mg/m^2 d1-2 + E 60 mg/m^2 d1-3 x 4	39 / 39	-	7.8	18	TS: 36%, TRD: 0 heme tox gr 3-4: 0
		67 (54%)	73 (70-79)	P 40 mg/m^2 d1-2 + E 100 mg/m^2 d1-3 + G-CSF x 4	69 / 9	-	10.3	39	TS: 63%, TRD: 1.5% heme tox gr 3-4: 10%
Eligibility: ≥ 70 years old; PS 0-2									
Okamoto 2007[110]	III	110 (0%)	74[a] (56-86)	C AUC 5 d1 + E 80 mg/m^2 d1-3 x 4	73 / 15	5.2	10.6[b]	41[c]	PSI: 63%, more platelet tox
		110 (0%)	74[d] (55-85)	P 25 mg/m^2 d1-3 + E 80 mg/m^2 d1-3 x 4	73 / 10	4.7 p=NS	9.9[e]	35[f] p=NS	PSI: 56%. similar non-heme tox
Eligibility: ≥ 70 years old and PS 0-1 (92%) OR < 70 years old and PS 3 (8%)									
Souhami 1997[111]	III	75 (10%)	67 (49-80)	E 100 mg po BID d1-5 x 6	33 / 5	3.6	4.8	10	worse QOL (p,0.01)
		80 (5%)	66 (50-86)	PE alternating with CAV x 6	46 / 10 p<0.01	5.6 p=0.001	5.9	19 p<0.05	more N/V, similar heme tox
Eligibility: ≥ 75 years old, any PS OR < 75 years old and PS 2-3 (unclear how many in each group; no separate analyses per age groups)									

E = etoposide; LD = limited disease; N/V = nausea/vomiting; P = cisplatin; PE = cisplatin + etoposide; PFS = progression-free survival; PSI = palliative score improvement; TS = therapeutic success (≥ 3 cycles at planned doses/schedule and objective response and no grade 3-4 nonhematologic toxicity or hematologic complications or hospitalizations/deaths due to toxicity). See Figures 3 and 4 for expansion of other abbreviations.

[a]93% ≥ 70 y old.

[b]10.8 mo in ≥ 70-y-old cohort.

[c]43% in ≥ 70-y-old cohort.

[d]91% ≥ 70 y old.

[e]10.1 mo in ≥ 70-y-old cohort.

[f]34% in ≥ 70-y-old cohort.

both younger and older patients, hematologic toxicity was greater in the elderly group and fewer patients completed the full course of therapy. Overall survival was better in younger patients, mainly because of a higher treatment-related death rate in elderly patients (10% vs 1%). Among elderly patients, trial results were reflective of the overall study findings, with better survival in those receiving bid radiation, although this improvement did not reach statistical significance in this small patient subset. Schild et al[113] performed a retrospective age analysis on NCCTG 89-20-52, a similar study that randomized 263 patients with LS-SCLC and a PS of 0 to 2 to standard PE with either once-daily or bid radiotherapy. In this trial, 21% of patients were ≥ 70 years old. Although both PFS and overall survival were somewhat lower in elderly patients, there were no significant differences in these end points between the younger and older patient subgroups. The incidence of severe pneumonitis (6% vs 0%, $P = .008$) and the incidence of treatment-related death (5.6% vs 0.5%, $P = .03$) were both significantly higher in elderly patients. Siu et al[114] reported a combined retrospective age analysis of two National Cancer Institute of Canada trials in patients with LS-SCLC and age ≤ 80 years with a PS of 0 to 3. Of the 608 patients enrolled in these trials, only 14% were ≥ 70 years old and 2% were ≥ 75 years old. Response rates and overall survival were similar between patients < 70 years old and those ≥ 70 years old, and age was not an independent prognostic factor in multivariate analysis. However, overall survival was significantly lower in the small subgroup of patients ≥ 75 years old. Again, elderly patients had a greater treatment-related death rate (4.5% vs 1.7%) despite receiving lower total drug doses. In a separate report, Quon et al[115] retrospectively analyzed the impact of age on radiation delivery, tolerance, and efficacy in the 458 patients in these two National Cancer Institute of Canada trials who received planned radiotherapy. They reported no statistical differences in any of these end points between patients < 70 years old and those ≥ 70 years old.

Based on the available data, it appears that platinum-based chemotherapy provides improved outcomes compared with lower-intensity regimens, with carboplatin and etoposide representing the most reasonable treatment option in elderly patients with SCLC. In patients with LS-SCLC, chemoradiotherapy appears to yield similar benefits in elderly and younger patients. Clearly, as with all medical therapy, treatment needs to be individualized based on patient characteristics, PS, and comorbidities.

8.1 Recommendations

8.1.1. In elderly patients with LS-SCLC and good PS (ECOG 0-2), treatment with platinum-based chemotherapy plus TRT is suggested, with close attention to management of treatment-related toxicity (Grade 2B)**.**

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

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

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Author contributions: Dr Jett had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Jett: contributed to the uniform development of the guidelines and contributions from each contributing author and is responsible for the final manuscript.

Dr Schild: contributed to the writing of all sections related to radiotherapy.

Dr Kesler: contributed to the writing of sections related to thoracic surgery.

Dr Kalemkerian: contributed to the writing of sections on utility of PET scan, staging, second-line therapy, and treatment in the elderly, and represented the authors of this guideline at the final conference for approval of the recommendations.

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