JAMA | Review

Small Cell Lung Cancer
A Review

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IMPORTANCE Small cell lung cancer (SCLC) is a high-grade neuroendocrine carcinoma with an incidence of 4.7 cases per 100 000 individuals in 2021 in the US and a 5-year overall survival of 12% to 30%.

OBSERVATIONS Cigarette smoking is the primary risk factor for development of SCLC, as 95% of patients diagnosed with SCLC have a history of tobacco use. Patients with SCLC may present with respiratory symptoms such as cough (40%), shortness of breath (34%), hemoptysis (10%), or metastases with corresponding local symptoms (30%) such as pleuritis or bone pain; approximately 60% of patients with SCLC may be asymptomatic at diagnosis. Chest imaging may demonstrate central hilar (85%) or mediastinal lymphadenopathy (75%). At diagnosis, approximately 15% of patients have brain metastases, which may present as headache or focal weakness. Diagnosis is confirmed by biopsy of a primary lung mass, thoracic lymph node, or metastatic lesion. Small cell lung cancer is classified into limited stage (LS-SCLC; 30%) vs extensive stage (ES-SCLC; 70%) based on whether the disease can be treated within a radiation field that is typically confined to 1 hemithorax but may include contralateral mediastinal and supraclavicular nodes. For patients with LS-SCLC, surgery or concurrent chemotherapy with platinum-etoposide and radiotherapy is potentially curative in 30% of patients. More recently, median survival for LS-SCLC has reached up to 55.9 months with the addition of durvalumab, an immunotherapy. First-line treatment for ES-SCLC is combined treatment with platinum-etoposide chemotherapy and immunotherapy with the programmed cell death 1 ligand 1 (PD-L1) inhibitors durvalumab or atezolizumab followed by maintenance immunotherapy until disease progression or toxicity. Although initial rates of tumor shrinkage are 60% to 70% with platinum-etoposide and immunotherapy treatment, the median overall survival of patients treated for ES-SCLC is approximately 12 to 13 months, with 60% of patients relapsing within 3 months. Second-line therapy for patients with ES-SCLC includes the DNA-alkylating agent lurbinectedin (35% overall response rate; median progression-free survival, 3.7 months) and a bispecific T-cell engager against delta-like ligand 3, tarlatamab (40% overall response rate; median progression-free survival, 4.9 months).

CONCLUSIONS AND RELEVANCE Small cell lung cancer is a smoking-related malignancy that presents at an advanced stage in 70% of patients. Three-year overall survival is approximately 56.5% for LS-SCLC and 17.6% for ES-SCLC. First-line treatment for LS-SCLC is radiation targeting the tumor given concurrently with chemotherapy and followed by consolidation immunotherapy. For ES-SCLC, first-line treatment is chemotherapy and immunotherapy followed by maintenance immunotherapy.

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In 2024, lung cancer was the leading cause of cancer-related mortality in the US and the second most commonly diagnosed cancer.[1] Small cell lung cancer (SCLC), previously referred to as "oat cell" carcinoma, represents 10% to 15% of all lung cancers, with an incidence of 4.7 per 100 000 individuals in 2021 in the US.[2] The incidence of SCLC has decreased over the last decade from 6.6 to 4.7 per 100 000 individuals, corresponding to a decrease in tobacco smoking over this period.[2]

Diagnosis is confirmed by biopsy of the primary tumor, involved thoracic lymph nodes, or metastatic lesion. Due to the high proliferative rate of SCLC, 70% of patients have advanced-stage disease at diagnosis.[2] The recommended treatment for patients with limited-stage (LS-SCLC) disease (stage I-III) is radiotherapy to the tumor and chemotherapy.[3] Patients with extensive-stage (ES-SCLC) disease (distant metastatic disease or disease that cannot be treated within a safe radiation field) should receive palliative care with combination chemotherapy and immunotherapy (**Figure**).

Treatment on relapse includes the DNA-alkylating agent lurbinectedin, re-treatment with platinum-etoposide chemotherapy, microtubule inhibitors such as taxanes, or alternative DNA-alkylating agents such as temozolomide. The US Food and Drug Administration (FDA) recently granted accelerated approval for tarlatamab, a bispecific antibody engaging in T cell–mediated destruction for relapsed SCLC. This Review summarizes the epidemiology, molecular characteristics, clinical presentation, and management of SCLC. Some common clinical questions and answers are shown in the **Box**.

Methods

We searched PubMed for articles with the term *small cell lung cancer*; the search was limited to English-language articles published between March 16, 2014, and October 13, 2024. Articles were selected with a focus on primary prospective data. A total of 95 articles were included. Articles comprised 24 randomized clinical trials, 2 long-term updates of randomized clinical trials, 2 secondary or pooled analyses of randomized clinical trials, 11 nonrandomized prospective trials, 1 update of a nonrandomized prospective trial, 11 meta-analyses and systematic reviews, 10 retrospective studies, 3 clinical practice guidelines, 3 reviews, and 9 translational studies. The remaining 19 articles were identified by the authors based on knowledge of the literature before 2014 and from review of citations in retrieved articles.

Discussion

Epidemiology

Approximately 16 000 new cases of SCLC were diagnosed in the US in 2024.[2] The median age at diagnosis in the US is 69 years, with a higher incidence in males compared with females (5.1 vs 4.6 cases per 100 000 individuals). Higher incidence of SCLC is observed among non-Hispanic American Indian and Alaska Native individuals (8.5 cases per 100 000 individuals), non-Hispanic Black individuals (3.9 cases per 100 000 individuals), and non-Hispanic White individuals (6.0 cases per 100 000 individuals) compared with non-Hispanic Asian and Pacific Islander individuals (1.9 cases per 100 000 individuals) or Hispanic individuals (2.2 cases per 100 000 individuals).[2] Small cell lung cancer is strongly associated with tobacco smoking (95% of patients with SCLC have a history of tobacco use), and although the risk of SCLC decreases with smoking cessation, incidence of SCLC remains elevated after quitting for more than 30 years.[4] Approximately 2.5% to 13% of SCLC has been reported in individuals who have never smoked, and these patients may have a better prognosis. Among 391 cases from a multicenter case-control study in South Korea, survival was 18.2 months among patients with no smoking history vs 13.1 months among people who smoked (P = .054).[5,6]

Molecular Characteristics of SCLC

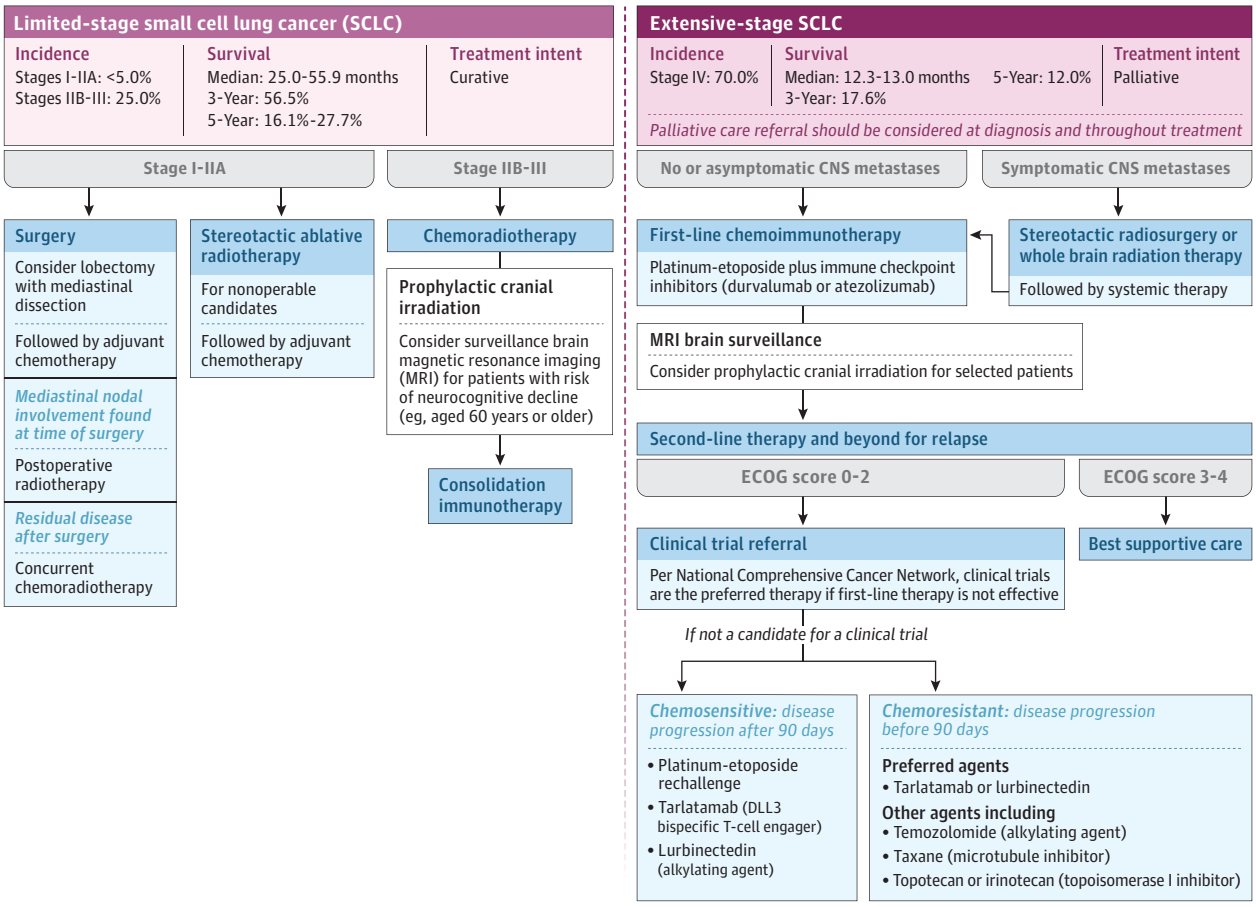
Small cell lung cancer is characterized by near universal loss of the tumor suppressor genes *RB1* and *TP53*,[7] and disease heterogeneity is characterized by expression of epigenetically regulated transcriptional factors. Subtypes include A and N, characterized by expression of neuroendocrine transcription factors *ASCL1* and *NeuroD1*, respectively, and subtype P, characterized by expression of non-neuroendocrine transcription factor *POU2F3*.[8] A fourth subtype, subtype I, is characterized by a lack of expression of *ASCL1*, *NeuroD1*, or *POU2F3* and has been characterized by expression of genes associated with response to immune checkpoint inhibitors, a class of drugs that block tumors from inactivating T cells (eFigure 1 in the Supplement).[9] *YAP1* has also been proposed as a potential subtype associated with upregulation of interferon-γ.[10] Unlike in non-SCLC, programmed cell death 1 ligand 1 (PD-L1), a surface glycoprotein expressed in tumor cells or antigen-presenting cells that allows tumor cells to escape immune destruction, is variably expressed in SCLC (0%-80%) and is not a predictive biomarker of response to checkpoint inhibitors in SCLC.[11,12]

Rarely, non-SCLC with genetic variants referred to as "oncogenic drivers," such as *EGFR* or *ALK* variants, that promote cancer growth may undergo histologic transformation from adenocarcinoma to SCLC, especially with tumors that also have *TP53* or *RB1* variants.[13,14] Such tumors are associated with decreased survival (6 to 8.5 months vs 13 months with de novo SCLC),[15,16] and mechanisms for the worse prognosis are poorly understood.[13,17]

Clinical Presentation

Patients with SCLC may present with cough (40%), shortness of breath (34%), or hemoptysis (10%), although up to 60% of patients may be asymptomatic. Pain at the site of disease involvement (30%) or constitutional symptoms such as weight loss (24%), anorexia (9%), and fatigue (15%) may be observed, especially in ES-SCLC.[18,19] Approximately 15% of patients with SCLC have brain metastases at diagnosis, which may present with headache or focal weakness. These patients have decreased survival compared with patients with ES-SCLC without brain metastases (6 months vs 13 months; P < .001).[20] Approximately 10% of patients present with superior vena cava syndrome, characterized by headaches, facial or neck swelling, upper extremity edema, or voice changes due to compression of the superior vena cava from adenopathy.[21] Patients with SCLC may also have paraneoplastic endocrinopathies, including syndrome of inappropriate antidiuretic hormone secretion (24% of SCLC) presenting with hyponatremia due to production of vasopressin, or Cushing syndrome (2%-6% of SCLC) presenting with edema, weakness, hypertension, or hypokalemia due to ectopic production of

Figure. Overview of Incidence and General Management of Limited-Stage SCLC and Extensive-Stage SCLC



CNS indicates central nervous system and ECOG, Eastern Cooperative Oncology Group. Staging is categorized as limited stage based on whether the disease is confined to 1 hemithorax and supraclavicular region that can be treated within a safe radiation field. Extensive stage includes patients with malignant pleural effusion or distant metastases or disease not classified as limited.

adrenocorticotropic hormone from the tumor.[22-24] Two to three percent of patients with SCLC may present with Lambert-Eaton myasthenic syndrome, characterized by muscle weakness, ataxia, and hyporeflexia from autoimmune destruction of voltage-gated calcium channels, which leads to impaired release of acetylcholine in the neuromuscular junction.[25,26]

Diagnostic Evaluation

Chest imaging with x-ray or computed tomography (CT) typically demonstrates a central, bronchial, or hilar mass with bulky adenopathy. Diagnosis is made by biopsy of the primary tumor and/or lymph nodes with an endoscopic bronchial ultrasound or by biopsy of a metastatic lesion. Pathologic diagnosis is confirmed by morphologic, immunohistochemical, and proliferative characteristics. Hematoxylin-eosin–stained slides of biopsied cytology or tissue demonstrate clusters of small, round, blue cells with a high nuclear to cytoplasm ratio and mitotic rate (≥10 mitoses per 10 high-power field).[18] Ki-67, or the proliferation index, which demonstrates how quickly a cell is dividing, typically ranges from 50% to 100%.[18] Immunohistochemistry stains of SCLC may be positive for cytokeratin (50%-60%), thyroid transcription factor 1 (80%), and neuroendocrine markers such as synaptophysin (54%), chromogranin A (37%), CD56 (90%-100%), and insulinoma-associated protein 1 (92%).[27-30] Small cell lung cancer may be distinguished from less-proliferative neuroendocrine tumors such as carcinoid and large cell neuroendocrine carcinomas by morphology and mitotic count as defined by the World Health Organization.[31]

Staging

For staging after diagnosis of SCLC, patients should undergo CT of the abdomen, brain magnetic resonance imaging (MRI), and positron emission tomography (PET)/CT. Bone scan may be used to rule out bone metastases if PET/CT is not available. Small cell lung cancer is classified as LS-SCLC or ES-SCLC based on whether the disease is confined to 1 hemithorax (with or without hilar nodal involvement) encompassed by 1 radiation portal.[32] The definition of LS-SCLC was expanded by the International Association for the Study of Lung Cancer in 1986 to include disease involving contralateral mediastinal and supraclavicular nodes and ipsilateral pleural effusion.[33,34] The TNM system, which stages tumors by primary tumor size, node positivity, and distant metastases, aligns closely with the International Association for the Study of Lung Cancer staging system and includes stages I through III (limited stage) and stage IV (extensive stage).[3]

Box. Clinical Questions and Answers

How Does SCLC Typically Present?

Approximately 60% of patients with small cell lung cancer (SCLC) are asymptomatic at presentation. However, SCLC may present with symptoms of cough, shortness of breath, or hemoptysis. Patients may also have bulky mediastinal adenopathy causing superior vena cava syndrome (10%) or brain metastases (15%). Paraneoplastic syndromes such as syndrome of inappropriate antidiuretic hormone secretion (25%), Cushing syndrome (2%-6%), or Lambert-Eaton myasthenic syndrome (2%-3%) may also occur in patients with SCLC.

What Are the First-Line Treatments for LS-SCLC and ES-SCLC?

First-line therapy for limited-stage (LS) SCLC is chemotherapy and radiotherapy followed by consolidation immunotherapy. Surgery followed by adjuvant chemotherapy can be considered for patients with LS-SCLC without lymph node involvement after multidisciplinary discussion with surgical, radiation, and medical oncology specialists. First-line therapy for extensive-stage (ES) SCLC is a combination of chemotherapy and immunotherapy, followed by maintenance immunotherapy.

What Are the Prognoses of LS-SCLC and ES-SCLC?

With treatment, the median overall survival is approximately 4.7 years for patients with LS-SCLC and approximately 13 months for patients with ES-SCLC. Three-year survival is currently approximately 56.5% for LS-SCLC and 17.6% for ES-SCLC. To improve quality of life and overall survival, all patients diagnosed with SCLC should establish care with a palliative care team, and patients with relapsed SCLC are encouraged to enroll in clinical trials, if available.

Treatment

Limited-Stage SCLC

First-Line Treatment

Limited-stage SCLC can be treated definitively with a combination of chemotherapy, local therapy such as radiation therapy or surgery, and consolidation immunotherapy with the goal of cure (**Table 1**). Multidisciplinary discussions involving oncologists, radiation oncologists, and thoracic surgeons can identify optimal treatment approaches and individualized care for patients with LS-SCLC.

Treatment for LS-SCLC is high-dose radiotherapy targeted to the primary tumor and involved lymph nodes concurrently with either cycle 1 or 2 of platinum-etoposide chemotherapy, administered for 4 to 6 cycles.[40] Initial response rates, defined as tumor reduction by at least 30%, are 70% to 90%.[36] Twice-daily radiation with 45 Gy in 30 fractions was previously established to have superior survival outcomes compared with once-daily radiotherapy with 45 Gy in 25 fractions.[35] Two phase 3 trials of patients with LS-SCLC compared twice-daily radiotherapy with once-daily high-dose radiotherapy (66-70 Gy in 33-35 fractions) and did not report superiority of once-daily high-dose radiotherapy (Table 1) in overall survival or adverse events (CONVERT trial [n = 547]: overall survival, 25 months for once-daily vs 30 months for twice-daily radiotherapy [hazard ratio, 1.18; 95% CI, 0.95-1.45]; CALGB 30610/RTOG 0538 trial [n = 638]: overall survival, 30.1 months for once-daily vs 28.5 months for twice-daily radiotherapy [hazard ratio, 0.94; 95% CI, 0.76-1.17]).[36,38] Given similar outcomes, once-daily or twice-daily radiotherapy regimens are reasonable, with the twice-daily regimen still considered first-line treatment because randomized trials have yet to show superiority in survival for a once-daily radiotherapy regimen. The twice-daily regimen may be appealing to those preferring a shorter treatment duration (3 weeks), and once-daily regimens (6.5-7 weeks) may be preferred based on factors such as transportation and radiotherapy machine availability.

Patients with node-negative (no lymph node involvement) stage I to IIA (T1-2N0M0) SCLC may be considered for thoracoscopic lobectomy if no tumor is detected in mediastinal and hilar lymph node biopsies. Fitness for resection is determined by evaluation of cardiac and pulmonary comorbidities (eg, pulmonary function testing).[41-43] Stereotactic body radiotherapy, a form of high-dose radiotherapy, is an effective and safe alternative to surgery for stage I to IIA (T1-2N0M0) disease.[44] After undergoing surgery or stereotactic body radiotherapy, patients are treated with adjuvant platinum-etoposide chemotherapy for 4 cycles.[43,45] For patients with positive resection margins, adjuvant radiation is recommended per National Comprehensive Cancer Network (NCCN) and American Society for Radiation Oncology (ASTRO) guidelines.[3,46] Evidence does not currently support neoadjuvant chemotherapy for SCLC.[47]

Consolidation Immunotherapy After Chemoradiation

Consolidation immunotherapy after chemoradiation is recommended per the NCCN for LS-SCLC.[47] The phase 3 ADRIATIC trial compared up to 2 years of consolidation durvalumab, an anti–PD-L1 inhibitor, given as monotherapy and in combination with tremelimumab, a checkpoint (cytotoxic T-lymphocyte–associated protein 4 [CTLA-4]) inhibitor, with placebo in 939 patients with inoperable stage I to III SCLC after chemoradiation.[39] The study reported improved overall survival and progression-free survival, defined as the time to disease progression or death with consolidation durvalumab relative to placebo (overall survival, 55.9 months with durvalumab vs 33.4 months with placebo [P = .01]; progression-free survival, 16.6 months with durvalumab vs 9.2 months with placebo [P = .02]).[39] Frequency of adverse events was reported as follows: any grade of adverse events possibly related to study treatment: 67.2% with durvalumab and 48.7% with placebo; grade 1 to 2 hypothyroidism: 14.9% with durvalumab and 3.4% with placebo; any grade of pneumonitis: 9.2% with durvalumab and 5.3% with placebo; and grade 3 to 4 pneumonitis: 1.1% with durvalumab and 0.8% with placebo (P values for comparisons not reported).[39]

Prophylactic Cranial Irradiation

Small cell lung cancer metastasizes to the brain in approximately 60% of patients within 3 years of LS-SCLC diagnosis.[48] Although prophylactic cranial irradiation is not typically administered to patients with early-stage LS-SCLC (stage I-IIA) due to limited survival advantage for these patients,[49,50] daily low-dose prophylactic cranial irradiation to the whole brain is recommended for patients with LS-SCLC (stage IIB-IIIC) on confirmation of tumor shrinkage on imaging following chemoradiation, per NCCN and ASTRO guidelines.[3,46] In a meta-analysis of 7 randomized trials of 987 patients with SCLC in complete remission, compared with no prophylactic cranial irradiation, prophylactic cranial irradiation

Table 1. Summary of Selected Phase 3 Randomized Clinical Trials for Limited-Stage Small Cell Lung Cancer[a]

Source	Regimen	Comparator	Primary end point	Outcome	Grade ≥3 adverse events	Clinical implications
Turrisi et al,[35] 1999 (n = 417)	Twice-daily radiotherapy to 45 Gy in 30 twice-daily fractions over 3 wk	Once-daily radiotherapy to 45 Gy in 25 once-daily fractions over 5 wk	Overall survival	Median, 23 mo vs 19 mo (hazard ratio, 0.83; *P* = .04)	Grade ≥3 esophagitis: 32.5% (twice-daily radiotherapy) vs 16.3% (once-daily radiotherapy)	Established twice-daily radiotherapy as standard of care vs low-dose daily radiotherapy
CONVERT,[36] 2017 (n = 547)	Once-daily radiotherapy to 66 Gy in 33 fractions over 6.5 wk	Twice-daily radiotherapy to 45 Gy in 30 twice-daily fractions over 3 wk	Overall survival	Median, 25 mo vs 30 mo (hazard ratio, 1.18; 95% CI, 0.95-1.45; *P* = .14)	Grade ≥3 esophagitis: 19% (once-daily radiotherapy) vs 18% (twice-daily radiotherapy); pneumonitis: 2.3% (once-daily radiotherapy) vs 1.9% (twice-daily radiotherapy)	No superiority of high-dose daily radiotherapy over twice-daily radiotherapy; outcomes generally appeared similar
PREMER,[37] 2021 (n = 150)	Hippocampal-sparing prophylactic cranial irradiation	Prophylactic cranial irradiation	No. of patients with delayed short-term memory at 3 mo	5.8% vs 23.5% (odds ratio, 5; 95% CI, 1.57-15.86; *P* = .003)	No grade ≥3 toxicities were observed in either group	Demonstrated hippocampal-sparing prophylactic cranial irradiation as an option to spare memory loss
CALGB 30610/RTOG 0538,[38] 2023 (n = 638)	Once-daily radiotherapy to 70 Gy in 35 fractions over 7 wk	Twice-daily radiotherapy to 45-Gy in 30 twice-daily fractions over 3 wk	Overall survival	Median, 30.1 mo vs 28.5 mo (hazard ratio, 0.94; 95% CI, 0.76-1.17; *P* = .59)	Grade ≥3 esophagitis: 17.5% (once-daily radiotherapy) vs 16% (twice-daily radiotherapy)	No superiority of high-dose daily radiotherapy over twice-daily radiotherapy; outcomes generally appeared similar
ADRIATIC,[39] 2024 (n = 530)	Chemoradiotherapy followed by consolidation durvalumab (programmed cell death 1 ligand 1 [PD-L1] inhibitor) for up to 2 y	Chemoradiotherapy followed by placebo	Overall survival, progression-free survival	Overall survival: median, 55.9 mo vs 33.4 mo (hazard ratio, 0.73; 95% CI, 0.57-0.93; *P* = .01); progression-free survival: median, 16.6 mo vs 9.2 mo (hazard ratio, 0.76; 95% CI, 0.61-0.95; *P* = .16)	Grade ≥3 treatment-emergent pneumonitis: 3.1% (durvalumab) vs 2.6% (placebo)	Established consolidation immunotherapy for up to 2 y after chemoradiotherapy

[a] Limited-stage disease is defined as confined to 1 hemithorax and supraclavicular region that can be treated within a safe radiation field. Studies are ordered by year of publication. Studies were selected based on quality and relevance to clinical care. Grade 3 adverse events are defined by National Cancer Institute Common Terminology Criteria for Adverse Events as severe or medically significant but not immediately life-threatening.

was associated with decreased cumulative incidence of brain metastases (58.6% vs 33.3%; *P* < .001) and an increase in overall survival at 3 years (15.3% vs 20.7%; *P* = .01).[48] A follow-up meta-analysis of 28 retrospective studies including 18 575 patients with LS-SCLC demonstrated an overall survival benefit associated with prophylactic cranial irradiation (overall survival, 27.8 months) vs without prophylactic cranial irradiation (overall survival, 18.8 months; pooled adjusted hazard ratio, 0.62; 95% CI, 0.57-0.69).[51]

Adverse effects from prophylactic cranial irradiation include increased risk of neurocognitive decline such as memory loss and decrease in executive function in up to 65% of patients at 6 months.[52] Memantine, an inhibitor of *N*-methyl-D-aspartate receptor, may be considered for 6 months during and after prophylactic cranial irradiation per NCCN guidelines, based on its association with decreased risk of cognitive decline at 24 weeks compared with placebo (53.8% vs 64.9%; *P* = .01).[52] Although hippocampal avoidance of radiation to bilateral hippocampi is recommended by the NCCN, studies have reported conflicting data about reducing risk of cognitive decline with this technique.[37,53,54] For patients who decline prophylactic cranial irradiation or do not undergo prophylactic cranial irradiation due to increased risk of neurocognitive decline (age ≥60 years or baseline neurocognitive impairment), close surveillance for brain metastases with brain MRI every 3 to 6 months is recommended per the NCCN.

Extensive-Stage SCLC

First-Line Treatment

First-line treatment for patients with ES-SCLC is chemotherapy with platinum-etoposide and an anti–PD-L1 inhibitor (atezolizumab or durvalumab) (**Table 2**). Two studies evaluating newly diagnosed ES-SCLC reported that addition of atezolizumab or durvalumab to chemotherapy, respectively, resulted in improved overall survival compared with platinum-etoposide chemotherapy alone. Addition of atezolizumab to platinum-etoposide chemotherapy resulted in a 2-month increased survival (10.3 vs 12.3 months; hazard ratio, 0.70; 95% CI, 0.54-0.91) at a median follow-up of 13.9 months (n = 403).[15] The addition of durvalumab to platinum-etoposide chemotherapy resulted in a similar increase in overall survival by 2.7 months (10.3 vs 13.0 months; hazard ratio, 0.73; 95% CI, 0.59-0.91) at a median follow-up of 18 months (n = 537).[15,16] Some patients had durable responses, with 3-year overall survival of 5.8% with placebo vs 17.6% with addition of durvalumab (hazard ratio, 0.71; 95% CI, 0.60-0.86) at a median follow-up of 39.4 months.[64] The incidence of treatment-related adverse events was similar in patients who received combination chemoimmunotherapy and chemotherapy, including grade 3 or higher adverse effects of neutropenia (23.2% with atezolizumab vs 24.5% with placebo; 23% with durvalumab plus chemotherapy vs 32% with chemotherapy alone), anemia (14.1% with atezolizumab vs 12.2% with placebo; 8% with durvalumab plus chemotherapy vs 14% with chemotherapy alone), and thrombocytopenia (10.1% with atezolizumab vs 7.7% with placebo; 5% with durvalumab plus chemotherapy vs 9% with chemotherapy).[15,16] The presence of anti–PD-1, expressed on T cells and a receptor for PD-L1, also has demonstrated clinical benefit as a target of therapy in some but not all studies.[55-57] Addition of other checkpoint inhibitors such as T-cell immunoglobulin and immunoreceptor tyrosine–based inhibitory motif domain (TIGIT), which inhibit activation and proliferation of T cells, to

Table 2. Summary of Selected Clinical Trials for Extensive-Stage Small Cell Lung Cancer[a]

Source	Trial type	Regimen	Comparator	Primary end point	Outcomes	Grade ≥3 AEs	FDA approval
First-line treatment							
IMpower133,[16] 2018 (n = 403)	Phase 3, randomized	Atezolizumab plus carboplatin-etoposide for 4 cycles, plus maintenance atezolizumab	Placebo plus carboplatin-etoposide for 4 cycles, plus maintenance placebo	Progression-free survival, overall survival	• Progression-free survival: 5.2 mo vs 4.3 mo (hazard ratio, 0.77; 95% CI, 0.62-0.96) • Overall survival: 12.3 mo vs 10.3 mo (hazard ratio, 0.70; 95% CI, 0.54-0.91)	• Grade ≥3 neutropenia: 23.2% (atezolizumab) vs 24.5% (placebo) • Grade ≥3 anemia: 14.1% (atezolizumab) vs 12.2% (placebo) • Grade ≥3 immune-mediated AE: 10.6% (atezolizumab) vs 2.6% (placebo)	2019
CASPIAN,[15] 2019 (n = 537)	Phase 3, randomized	Durvalumab plus platinum-etoposide up to 4 cycles, plus maintenance durvalumab	Platinum-etoposide for up to 6 cycles with or without prophylactic cranial irradiation	Overall survival	13 mo vs 10.3 mo (hazard ratio, 0.73; 95% CI, 0.59-0.91)	• Grade ≥3 neutropenia: 24% (durvalumab plus platinum-etoposide) vs 33% (platinum-etoposide) • Grade ≥3 anemia: 9% (durvalumab plus platinum-etoposide) vs 18% (platinum-etoposide) • Grade ≥3 immune-mediated AE: 5% (durvalumab plus platinum-etoposide) vs <1% (platinum-etoposide)	2020
KEYNOTE-604,[55] 2020 (n = 453)	Phase 3, randomized	Pembrolizumab plus platinum-etoposide for 4 cycles plus maintenance pembrolizumab	Platinum-etoposide for 4 cycles plus maintenance placebo	Progression-free survival, overall survival	• Progression-free survival: 4.5 mo vs 4.3 mo (hazard ratio, 0.75; 95% CI, 0.61-0.91) • Overall survival: 10.8 mo vs 9.7 mo (hazard ratio, 0.80; 95% CI, 0.64-0.98; *P* = .02)	• Grade ≥3 neutropenia: 43.5% (pembrolizumab) vs 40.8% (placebo) • Grade ≥3 anemia: 15.7% (pembrolizumab) vs 15.2% (placebo) • Grade ≥3 immune-mediated AE: 7.2% (pembrolizumab) vs 0.9% (placebo)	Not FDA approved
ASTRUM-005,[56] 2022 (n = 585)	Phase 3, randomized	Serplulimab plus carboplatin-etoposide for up to 4 cycles plus maintenance serplulimab	Placebo plus carboplatin-etoposide for up to 4 cycles plus maintenance placebo	Overall survival	15.4 mo vs 10.9 mo (hazard ratio, 0.63; 95% CI, 0.49-0.82; *P* < .001)	• Grade ≥3 neutropenia: 14.1% (serplulimab) vs 13.8% (placebo) • Grade ≥3 anemia: 5.4% (serplulimab) vs 5.6% (placebo) • Grade ≥3 immune-mediated AE: 9.5% (serplulimab) vs 5.6% (placebo)	Approved in China, 2022
CAPSTONE-1,[57] 2022 (n = 462)	Phase 3, randomized	Adebrelimab plus carboplatin-etoposide for 6 cycles plus maintenance adebrelimab	Placebo plus carboplatin-etoposide for 6 cycles plus maintenance placebo	Overall survival	15.3 mo vs 12.8 mo (hazard ratio, 0.72; 95% CI, 0.58-0.90; *P* = .002)	• Grade ≥3 neutropenia: 76% (adebrelimab) vs 75% (placebo) • Grade ≥3 anemia: 28% (adebrelimab) vs 28% (placebo) • Grade ≥3 immune-mediated AE: 4.8% (adebrelimab) vs 3% (placebo)	Approved in China, 2023
ETER701,[58] 2024 (n = 738)	Phase 3, randomized	Benmelstobart plus anlotinib plus carboplatin plus etoposide or placebo plus anlotinib plus carboplatin plus etoposide	Placebo plus placebo plus carboplatin plus etoposide	Progression-free survival, overall survival	• Progression-free survival: 6.9 mo vs 4.2 mo (hazard ratio, 0.32; 95% CI, 0.26-0.41; *P* < .001) • Overall survival: 19.3 mo vs 11.9 mo (hazard ratio, 0.61; 95% CI, 0.47-0.79; *P* < .001)	• Grade ≥3 neutropenia: 69.9% (benmelstobart plus anlotinib plus carboplatin plus etoposide) vs 68.7% (placebo plus placebo plus carboplatin plus etoposide) • Grade ≥3 thrombocytopenia: 49.6% (benmelstobart plus anlotinib plus carboplatin plus etoposide) vs 35.8% (placebo plus placebo plus carboplatin plus etoposide) • Grade ≥3 anemia: 25.2% (benmelstobart plus anlotinib plus carboplatin plus etoposide) vs 24.0% (placebo plus placebo plus carboplatin plus etoposide) • Grade ≥3 hypertension: 15.9% (benmelstobart plus anlotinib plus carboplatin plus etoposide) vs 2.4% (placebo plus placebo plus carboplatin plus etoposide) • Grade ≥3 proteinuria: 0.8% (benmelstobart plus anlotinib plus carboplatin plus etoposide) vs 0.4% (placebo plus placebo plus carboplatin plus etoposide)	Not FDA approved

(continued)

Table 2. Summary of Selected Clinical Trials for Extensive-Stage Small Cell Lung Cancer[a] (continued)

Source	Trial type	Regimen	Comparator	Primary end point	Outcomes	Grade ≥3 AEs	FDA approval
Maintenance							
SWOG S1929,[59] 2023 (n = 106)	Phase 2, randomized	Maintenance talazoparib plus atezolizumab	Maintenance atezolizumab	Progression-free survival	4.2 mo vs 2.8 mo (hazard ratio, 0.70; 80% CI, 0.52-0.94)	Grade 3 anemia: 37% (talazoparib plus atezolizumab) vs 2% (atezolizumab)	Not FDA approved
Relapse							
Trigo et al,[60] 2020 (n = 105)	Phase 2, single-group basket	Lurbinectedin, 3.2 mg/m^2	Not applicable	Overall response rate	35.2%	• Grade ≥3 neutropenia: 46% • Grade ≥3 anemia: 9% • Grade ≥3 thrombocytopenia: 7%	Accelerated FDA approval, 2020
Baize et al,[61] 2020 (n = 164)	Phase 3, randomized	Carboplatin-etoposide for 6 cycles	Oral topotecan for 6 cycles	Progression-free survival	4.7 mo vs 2.7 mo (hazard ratio, 0.57; 90% CI, 0.41-0.73)	• Grade ≥3 neutropenia: 13.6% (chemotherapy) vs 24.7% (topotecan) • Grade ≥3 anemia: 30.9% (chemotherapy) vs 35.8% (topotecan) • Grade ≥3 thrombocytopenia: 24.7% (chemotherapy) vs 21% (topotecan) • Grade ≥3 febrile neutropenia: 6.2% (chemotherapy) vs 13.6% (topotecan)	Recommended per NCCN guidelines
ATLANTIS,[62] 2023 (n = 613)	Phase 3, randomized	Lurbinectedin, 2.0 mg/m^2, plus doxorubicin	Physician choice of topotecan or cyclophosphamide, doxorubicin, and vincristine	Overall survival	8.6 mo vs 7.6 mo (hazard ratio, 0.97; 95% CI, 0.82-1.15)	• Grade ≥3 neutropenia: 37% (lurbinectedin plus doxorubicin) vs 69% (control) • Grade ≥3 anemia: 19% (lurbinectedin plus doxorubicin) vs 38% (control) • Grade ≥3 thrombocytopenia: 14% (lurbinectedin plus doxorubicin) vs 31% (control)	Combination not FDA approved
DeLLphi-301,[63] 2023 (n = 220)	Phase 2, single-group	Tarlatamab	Not applicable	Overall response rate	40% with 10 mg; 32% with 100 mg	• Cytokine-release syndrome: 51%; grade ≥3, 0.75% (10-mg subgroup) • Immune effector cell-associated neurotoxicity syndrome: 8.3%; grade ≥3: 0% (10-mg subgroup) • Grade ≥3 neutropenia: 6.0%	Accelerated FDA approval, 2024

Abbreviations: AE, adverse event; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network.

[a] Extensive-stage small cell lung cancer is defined as disease extending beyond a single hemithorax or disease extending beyond a single radiation field for treatment. Trials are ordered by year of publication per type of treatment. Studies were selected based on quality and relevance to clinical care.

combination platinum-etoposide and anti–PD-1 therapy has not demonstrated a survival benefit in patients with ES-SCLC.[65]

Maintenance Therapy

After initial cytoreduction with chemoimmunotherapy, monthly maintenance therapy with atezolizumab or durvalumab until tumor progression and/or treatment intolerance is recommended for patients with ES-SCLC per NCCN guidelines to prolong control of tumor growth.[15,16] Most patients with ES-SCLC have regrowth of tumor after prior tumor shrinkage or development of new metastases on imaging within 3 to 4 months of initiation of maintenance treatment, and maintenance therapies with nivolumab (an anti–PD-1 inhibitor) or nivolumab with ipilimumab (an anti–CTLA-4 inhibitor) have not improved overall survival.[66] Additional maintenance strategies with poly–adenosine diphosphate ribose polymerase (PARP) inhibitors[59] and delta-like ligand 3–targeting antibody drug conjugates[67] have also not demonstrated survival benefit in patients with ES-SCLC.

Consolidative thoracic radiation, radiation given within 6 weeks after initial chemotherapy or chemoimmunotherapy, may be used to treat residual or persistent intrathoracic disease in patients with ES-SCLC who have initial tumor reduction or tumor stability on imaging with platinum-etoposide therapy.[46] In a trial of 495 patients with ES-SCLC who had tumor shrinkage with induction chemotherapy, low-dose consolidative thoracic radiotherapy of 30 Gy in 10 fractions given with chemotherapy conferred a 2-year overall survival benefit compared with chemotherapy alone (13% vs 3%; $P = .004$).[68] The most common serious adverse effects were fatigue (4.5%) and shortness of breath (1.2%).[68] There are limited prospective data on the efficacy of consolidative radiation after chemoimmunotherapy. Consolidative thoracic radiation may be considered for patients with ES-SCLC who have residual or persistent intrathoracic disease after chemoimmunotherapy per ASTRO guidelines.[15,16,46]

Prophylactic Cranial Irradiation

Prophylactic cranial irradiation for ES-SCLC is controversial. Based on NCCN and ASTRO guidelines, either prophylactic cranial irradiation or brain MRI surveillance every 3 to 6 months can be considered; MRI surveillance is used more commonly than prophylactic cranial irradiation in current clinical practice in the US.[3,46,69,70] A phase 3 trial of 224 patients with ES-SCLC without brain metastases who had tumor shrinkage after treatment with platinum-etoposide chemotherapy did not demonstrate a survival benefit with prophylactic cranial irradiation compared with close MRI surveillance (every 3 months for up to 12 months followed by 18 and 24 months after enrollment), with overall survival of 11.6 months with prophylactic cranial irradiation and 13.7 months with MRI surveillance (hazard ratio, 1.27; 95% CI, 0.96-1.68).[70]

Relapse

Second-Line Treatment/Relapsed SCLC

Approximately 50% of patients relapse after 9 months of concurrent chemoradiation for LS-SCLC and after 4 to 5 months of maintenance immunotherapy for ES-SCLC.[15,16,39] Survival upon progression or relapse is 3 to 4 months without treatment.[71] Poor prognosis despite initial response to first-line therapy may be due to the clonal diversity of SCLC that emerges after treatment, which may confer resistance mechanisms that are difficult to target with 1 class of drug.[72] Clinical trial enrollment for all patients upon relapse is strongly recommended by NCCN guidelines. If clinical trials are not available, per the NCCN the recommended subsequent therapy after progression with first-line therapy depends on tumor sensitivity to chemotherapy, assessed by how long a patient has maintained tumor shrinkage without subsequent chemotherapy (Table 2). In a randomized phase 3 trial of 162 patients with ES-SCLC who had disease progression or relapse after 90 days of treatment with platinum-etoposide, re-treatment with platinum-etoposide improved progression-free survival compared with topotecan (4.7 vs 2.7 months; hazard ratio, 0.57; 90% CI, 0.41-0.73), with lower frequency of neutropenia (14% vs 22%) and febrile neutropenia (6% vs 11%).[61] Re-treatment with platinum-etoposide chemotherapy can be considered for relapsing patients who had a prior treatment response of greater than 6 months to first-line platinum-etoposide chemotherapy.[3]

For patients who had a poor prior treatment response to platinum-etoposide, lurbinectedin, a DNA-alkylating agent, is an FDA-approved second-line therapy for SCLC. In a single-group phase 2 trial, lurbinectedin had an overall response rate (tumor shrinkage of at least 30%) in 35.2% (95% CI, 26.2%-45.2%) of 105 previously treated patients with SCLC without brain metastases.[60] In patients with a chemotherapy-free treatment interval of 180 days or longer, the overall response rate with lurbinectedin was 60% (95% CI, 36.1%-86.9%).[73] The phase 3 ATLANTIS trial (n = 613) did not demonstrate improved survival with lurbinectedin in combination with doxorubicin compared with physician choice of topotecan or cyclophosphamide/doxorubicin/vincristine (Table 2), with negative results attributed to a lower dose of lurbinectedin used in combination with doxorubicin relative to standard monotherapy dosing.[62]

Alternative second-line treatments for ES-SCLC include topotecan,[74] irinotecan-based therapy,[75-77] taxanes,[78-80] temozolomide,[81] and gemcitabine-based therapies.[78] Tarlatamab, a bispecific T-cell engager against immune T cells and delta-like ligand 3, a transmembrane protein abnormally expressed in 85% to 94% of SCLC, recently gained accelerated FDA approval for patients with SCLC who progress despite treatment with platinum-etoposide chemotherapy and immunotherapy.[63] In a phase 2 trial of 220 patients with ES-SCLC, tarlatamab led to an overall response rate, defined as at least 30% tumor reduction from baseline, of 40% with a 10-mg dose and 32% with a 100-mg dose.[63] Fifty-nine percent of patients had a treatment response for 6 months or longer, and 68% of patients taking the 10-mg dose had a 9-month overall survival of 68%.[63] Grade 1 or 2 cytokine-release syndrome, a systemic inflammatory syndrome characterized by sudden release of cytokines, which presents as fever with or without hypotension or hypoxia, was observed in at least half of patients and was treatable.[63] Future directions for SCLC treatment include tailored approaches targeting DNA repair pathways, surface proteins expressed in SCLC such as seizure-related 6 homologue (SEZ6)[82,83] or B7H3,[84] and immune modulation such as inhibiting lysine-specific demethylase 1 (LSD1),[85] which enhances antigen presentation to immune cells (eFigures 1 and 2 in the Supplement).

Brain Metastases in ES-SCLC

Chemoimmunotherapy penetrates the blood-brain barrier and is the recommended initial approach per the NCCN for patients with

ES-SCLC with asymptomatic brain metastases. For patients with neurologic symptoms such as headache, nausea, or vomiting, dexamethasone, 4 mg every 6 hours, and stereotactic radiosurgery or whole-brain radiotherapy prior to systemic therapy is recommended.[3] Brain metastases that develop after initiation of systemic therapy in ES-SCLC have conventionally been treated with whole-brain radiation. However, gamma-knife radiation, a type of stereotactic radiosurgery that provides precise high-dose radiation to the tumor, may also be used and is increasingly preferred due to decreased risk of neurocognitive decline.[86] For selected patients with an isolated large, symptomatic brain metastasis, craniotomy and resection of the metastasis may be considered.

A cohort study of patients with ES-SCLC with brain metastases compared treatment with stereotactic radiosurgery (n = 710) vs whole-brain radiation (n = 219).[87] Although whole-brain radiation was associated with a longer time to central nervous system progression, defined as time from radiation to development of new central nervous system lesions, overall survival was greater with stereotactic radiosurgery vs whole-brain radiation (6.5 months vs 5.2 months; *P* = .003).[87] However, a subsequent meta-analysis of 7 retrospective studies that included 18 050 patients with SCLC with brain metastases reported similar overall survival (hazard ratio, 0.87; 95% CI, 0.76-1.01) among patients receiving whole-brain radiation therapy and stereotactic radiosurgery.[88] The threshold for the number of brain metastases indicated for stereotactic radiosurgery over whole-brain radiation has not been prospectively established; stereotactic radiosurgery may be considered for 10 or fewer brain metastases.[86,87]

Prognosis

For patients with LS-SCLC, 5-year overall survival with chemotherapy and radiation therapy was 16.1% to 27.7%[2] prior to introduction of durvalumab. With the addition of 2 years of consolidation durvalumab, overall survival for LS-SCLC has improved from a median of 33.4 months to 55.9 months, with 3-year overall survival of 56.5%.[39] Patients with ES-SCLC have an initial response rate of approximately 60% to 80% to chemoimmunotherapy, with 3-year overall survival of 17.6% and 5-year overall survival of 12%.[15,16,64,89]

Practical Considerations

Treatment of Superior Vena Cava Syndrome

First-line treatment for symptomatic superior vena cava syndrome is chemotherapy.[90] Patients with superior vena cava syndrome who have dyspnea, dysphagia, or cyanosis may also be treated with dexamethasone, 4 mg every 6 hours, or radiation if chemotherapy cannot be initiated expeditiously. Stenting is typically not recommended as initial therapy for superior vena cava syndrome as SCLC is responsive to chemotherapy and radiation.

Treatment of Paraneoplastic Syndromes

For patients with paraneoplastic Cushing syndrome, steroidogenesis inhibitors such as ketoconazole may be used if Cushing syndrome does not improve with chemoimmunotherapy. Patients with syndrome of inappropriate antidiuretic hormone secretion may be treated with fluid restriction, and if not improved, salt tablets, demeclocycline (tetracycline antibiotic), or tolvaptan can be considered.[3,22] Lambert-Eaton syndrome may be treated with intravenous immunoglobulin or amifampridine (potassium channel blocker).[25,91]

Treatment With Palliative Radiotherapy

Palliative radiotherapy may be considered for patients with SCLC who have airway compromise due to tumor mass effect, clinically significant hemoptysis due to vascular involvement of tumor, or extracranial metastases associated with pain or spinal cord compromise.[3]

Chemotherapy-Induced Myelosuppression

Chemotherapy-induced myelosuppression, which may present with anemia, thrombocytopenia, or neutropenia, is usually managed with prophylactic granulocyte colony-stimulating factor after completion of each cycle of chemotherapy. Another option to prevent myelosuppression is trilaciclib, a cyclin-dependent kinase 4/6 inhibitor, which arrests hemopoietic progenitor cells in the G1 stage of the cell cycle. In a pooled analysis of 242 patients with ES-SCLC, trilaciclib, administered as a 30-minute infusion within 4 hours prior to chemoimmunotherapy or prior to every cycle of chemotherapy, reduced the use of granulocyte colony-stimulating factor (28.5% vs 56.3% with placebo; *P* < .001), erythropoiesis-stimulating agents (3.3% vs 11.8% with placebo; *P* = .03), and red blood cell transfusion (14.6% vs 26.1%; *P* = .03).[92]

Tumor Lysis Syndrome

Due to rapid apoptosis of tumor cells with chemotherapy, patients with ES-SCLC may develop tumor lysis syndrome, which may result in electrolyte imbalances. Therefore, potassium, phosphate, calcium, uric acid, and kidney function should be closely monitored in patients with ES-SCLC who are starting chemotherapy. Patients with signs of active tumor lysis should be hospitalized to treat electrolyte imbalances and for close monitoring of cardiac and kidney function. Prophylaxis with allopurinol is not usually indicated for patients with normal or mildly elevated uric acid. Allopurinol and rasburicase, a urate oxidase enzyme that transforms uric acid into an inactive metabolite, may be indicated for patients with spontaneous tumor lysis syndrome (signs of tumor lysis prior to initiating chemotherapy).

Palliative Care

Given the poor prognosis of SCLC, all patients should establish care with a palliative care team at the time of diagnosis. Early palliative care has been associated with improved physical, functional, emotional, and social well-being in patients with lung cancer as assessed by the Functional Assessment of Cancer Therapy–Lung scale (score range, 0-136, with higher scores reflecting improved quality of life; clinically meaningful change is 2-3 points) (score, 98 vs 91.5; *P* = .03) and improved survival (11.6 months vs 8.9 months; *P* = .02).[93,94] Patients with SCLC should have ongoing conversations about goals of care including desire for cardiopulmonary resuscitation and mechanical ventilation, and consideration of hospice as an alternative to treatment.

Limitations

This Review has limitations. First, it may have missed some relevant articles. Second, a formal quality assessment of the included literature was not performed. Third, due to the poor prognosis of SCLC and challenges in patient recruitment, there are few randomized phase 3 treatment trials for SCLC.

Conclusions

Small cell lung cancer is a smoking-related malignancy that presents at an advanced stage in 70% of patients. Three-year overall survival is approximately 56.5% for LS-SCLC and 17.6% for ES-SCLC. Treatment for LS-SCLC is once- or twice-daily radiation targeting the tumor, given concurrently with chemotherapy, followed by consolidation immunotherapy for 2 years. First-line treatment for ES-SCLC is a combination of chemotherapy and immunotherapy followed by maintenance immunotherapy. Participation in clinical trials, if available, should be encouraged, and palliative care is associated with improvements in quality of life and overall survival for patients with SCLC.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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