SPECIAL ARTICLE

American Radium Society Appropriate Use Criteria on Radiation Therapy for Extensive-Stage SCLC

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ABSTRACT

Introduction: The standard-of-care therapy for extensive-stage SCLC has recently changed with the results of two large randomized trials revealing improved survival with the addition of immunotherapy to first-line platinum or etoposide chemotherapy. This has led to a lack of clarity around the role of consolidative thoracic radiation and prophylactic cranial irradiation in the setting of chemoimmunotherapy.

Methods: The American Radium Society Appropriate Use Criteria are evidence-based guidelines for specific clinical conditions that are reviewed by a multidisciplinary expert panel. The guidelines include a review and analysis of current evidence with the application of consensus methodology (modified Delphi) to rate the appropriateness of treatments recommended by the panel for extensive-stage SCLC.

Results: Current evidence supports either prophylactic cranial irradiation or surveillance with magnetic resonance imaging every 3 months for patients without evidence of brain metastases. Patients with brain metastases should receive whole-brain radiation with a recommended dose of 30 Gy in 10 fractions. Consolidative thoracic radiation can be considered in selected cases with the recommended dose ranging from 30 to 54 Gy; this recommendation was driven by expert opinion owing to the limited strength of evidence, as clinical trials addressing this question remain ongoing.

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Conclusions: Radiation therapy remains an integral component in the treatment paradigm for ES-SCLC.

Keywords: Small cell lung cancer; Extensive stage; Thoracic radiation; Appropriateness criteria; Prophylactic cranial irradiation

Introduction

SCLC comprises 13% of all lung cancers, and most are diagnosed at an advanced, extensive stage.[1] The cornerstone of treatment for extensive-stage SCLC (ES-SCLC) is four to six cycles of platinum or etoposide chemotherapy, with median survival ranging from 6 to 12 months.[2] Recent studies have found a modest improvement in median overall survival with the addition of immunotherapy to systemic therapy in the first-line setting.[3,4] Although the response to first-line systemic therapy for ES-SCLC is typically robust, the progression of disease after initial response to systemic therapy is nearly uniform and most often happens within the first 6 months of first-line therapy completion, resulting in poor long-term clinical outcomes.[5-7] Unfortunately, the response rates to second-line therapies are typically less than 10%.[8] In one large randomized trial, prophylactic cranial irradiation (PCI) has been reported to improve overall survival (OS) in patients with at least a partial response to systemic therapy[9]; however, a separate randomized trial in which brain magnetic resonance imaging (MRI) was repeated after chemotherapy and during follow-up found no benefit to PCI.[10] Thoracic radiation has also improved the 2-year OS in the CREST study,[11] but another randomized trial failed to exhibit a survival benefit to consolidative thoracic radiation.[12] The American Radium Society Appropriate Use Criteria presented in this manuscript are evidence-based guidelines for the treatment of ES-SCLC that have been created by a panel of lung cancer experts. The authors discuss the controversies and clinical issues around PCI, consolidative thoracic radiation, and immunotherapy in the management of ES-SCLC, and they provide evidence-based recommendations for different clinical scenarios, with the goal of guiding radiation oncologists on the optimal clinical management of ES-SCLC.

Materials and Methods

A literature review was conducted on peer-reviewed journals using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] The PubMed database was queried to retrieve all pertinent articles that included keywords including "extensive-stage small cell lung cancer," "PCI," and "consolidative thoracic radiation," using no date restrictions and including all articles through June 2020. Bibliographies of full articles were also reviewed for comprehensiveness with relevant studies included. Articles were reviewed for quality of study design, study size, methodology, and selection bias. Case reports or unpublished data were excluded.

The Modified Delphi method[14] (a well-established consensus methodology) was used by the expert panel to rate the appropriateness of treatment recommendations. The expert panel was composed of radiation oncologists, medical oncologists, and thoracic surgeons with expertise in the treatment of lung cancer.

Methodology

An analysis of the medical literature from peer-reviewed journals was conducted from 1970 to 2019 of the PubMed database to retrieve a comprehensive set of relevant articles. The search strategy was developed on the basis of the National Library of Medicine Medical Subject Headings with the addition of subject-specific keywords. Owing to the broad scope of medical literature on ES-SCLC, the expert panel composed of multidisciplinary radiation, medical, and surgical oncologists and additional members with subject-specific expertise reviewed pertinent studies and excluded studies that were not relevant or that they determined were of lower impact or quality. The literature was reviewed for quality of study design, cohort size, selection bias, evaluation of participants in relation to time from exposure, and methods of assessments. A well-established methodology (modified Delphi) was used by the expert panel to rate the appropriate use of procedures.

Summary of Evidence

Of the 36 references cited, there were 13 well-designed studies, three moderately well-designed studies, six studies with design limitations, two meta-analyses, and 12 studies that were not classified as primary references. These references were published between 1981 and 2020.

Supporting Documents

For additional information on the ARS Appropriate Use Criteria methodology and other supporting documents, go to http://www.americanradiumsociety.org/page/aucmethodology. The American Radium Society Appropriate Use Criteria and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of the specified medical condition(s). These criteria are intended to guide

treating and referring physicians in making decisions regarding the diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient's condition are ranked. Other procedures necessary to evaluate or treat other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the U.S. FDA have not been considered in developing these criteria; however, the study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in the light of all the circumstances presented in an individual examination.

Prophylactic Cranial Irradiation

PCI has been used as a means of preventing brain metastases in both limited-stage and ES-SCLC for several decades owing to the underlying assumption of poor penetrance of chemotherapy across the blood-brain barrier. Previous reports indicate a 60% to 70% risk of development of brain metastases after chemotherapy in patients who do not receive PCI.[15] Two meta-analyses have studied the role of PCI in limited-stage and ES-SCLC, with both exhibiting a reduction in the incidence of brain metastases and an improvement in OS.[16,17] The meta-analysis by Aupérin et al.[16] revealed a 5.4% absolute survival advantage at 3 years in patients who received PCI after a complete response to first-line chemotherapy. The studies included in these meta-analyses, conducted from the 1960s to 1990s, included patients receiving a variety of imaging modalities, including computed tomography (CT), scintigraphy, or no imaging. MRI, the currently accepted standard to detect brain metastases, was not typically performed during this era. The generalizability of these studies to current clinical practice is questioned, given the standard practice now to obtain MRI for a complete staging workup and the improvements in systemic therapies, including the benefit of immunotherapy plus chemotherapy in the first-line setting.

The most modern randomized trials addressing PCI in the ES-SCLC setting are the European Organization for Research and Treatment of Cancer (EORTC)[9] and Japanese[10] studies, which report conflicting results. In the EORTC study, published in 2011, randomized patients with any response to chemotherapy either received PCI with a dose of 20 to 30 Gy delivered in four to 12 fractions or observation. Patients underwent brain imaging (CT or MRI) after chemotherapy only if neurologic symptoms were present before PCI and in follow-up (to include symptoms of increased intracranial pressure, headache, nausea or vomiting, seizures, or focal neurologic symptoms). Findings included significant improvements in 1-year survival in the PCI group (27.1% versus 13.3%), and a significant reduction in the cumulative risk of brain metastases within 1 year (14.6% versus 40.4%).[9]

The most recent randomized trial in ES-SCLC testing PCI was published in 2017. This study, performed in Japan, enrolled patients with any response to systemic therapy and no evidence of brain metastases on MRI. Patients received either PCI with a dose of 25 Gy in 10 fractions or observation. Patients randomized to observation were required to undergo brain MRI every 3 months for 1 year and every 6 months until 24 months after enrollment. A total of 69% of patients in the observation arm ultimately developed brain metastases; the cumulative incidences of brain metastases were significantly lower at 6, 12, and 18 months for PCI compared with observation (15% versus 46.2%, 32.9% versus 59%, and 40.1% versus 63.8%, respectively). However, OS at 1 year was 48.4% in the PCI group and 53.6% in the observation group; the median survival for PCI was 11.6 months compared with 13.7 months in the observation arm (hazard ratio [HR]: 1.27, $p = 0.094$).[10] The pertinent trials studying PCI in ES-SCLC are summarized in Table 1.

The above studies reveal two significant findings: (1) PCI improves survival in a patient population that does not undergo routine MRI surveillance to detect brain metastases, and (2) PCI does not seem to improve survival in patients who undergo frequent brain MRI surveillance and receive timely salvage radiation for brain metastases. A SWOG study, S1827 or the MAVERICK study (NCT04155034), is further evaluating the concept of close MRI surveillance in lieu of PCI in both limited-stage and ES-SCLC in a North American population. More importantly, this study will be conducted in the era of immunotherapy usage in ES-SCLC, which is a stratified variable of the study. This study is currently accruing throughout the United States and Canada and will further clarify the role of PCI in ES-SCLC.

When PCI is delivered, 25 Gy is recommended per the results of EORTC 22003-08004, which tested the standard dose (25 Gy in 10 fractions) compared with high dose (36 Gy, delivered in 18–24 fractions) PCI in patients with limited-stage SCLC. No significant increase in brain metastases at 2 years was observed in the standard-dose

Table 1. Seminal Completed and Ongoing Studies in PCI for SCLC

Reference	Study Type	Patients	Study Objective (Purpose of Study)	Study Results
1. Takahashi et al. 2017[10]	Phase 3	224	To test PCI vs. MRI surveillance in patients with ES-SCLC	Median OS 11.6 mo (95% CI: 9·5-13·3) in the PCI group compared with 13.7 mo in the observation group (HR: 1·27, 95% CI: 0·96-1·68; $p = 0·094$).
2. Slotman et al. 2007[9]	Phase 3	286	To determine if PCI improves OS in patients with ES-SCLC who respond to chemotherapy	Median OS from 5.4 mo in the control group compared with 6.7 mo in the PCI arm. The 1-year survival rate was 27.1% (95% CI: 19.4-35.5) in the PCI arm and 13.3% (95% CI: 8.1-19.9) in the control group.
3. Le Pechoux et al. 2009[18]	Phase 3	720	The objective of this study was to determine the optimal dose of PCI	No significant dierence in the 2-year incidence of brain metastases between the standard PCI dose group and the higher-dose group, at 29% and 23%, respectively (HR: 0·80 [95% CI 0·57-1·11], $p = 0·18$). 2-year OS was 42% in the standard-dose group and 37% in the higher-dose group (HR: 1·20 [1·00-1·44]; $p = 0·05$).
4. NRG Oncology CC003 (NCT02635009); PI: Gondi V	Phase 2/3	392	To determine the rate of neurocognitive decline (measured by HVLT-R) and intracranial relapse of PCI alone vs. PCI with hippocampal avoidance	Actively recruiting. Results pending.
5. SWOG 1827 (NCT04155034); PI: Rusthoven K	Phase 3	668	To determine OS in patients receiving MRI surveillance alone or MRI surveillance and PCI	Actively recruiting. Results pending.

CI, confidence interval; EC-SCLC, extensive-stage SCLC; HR, hazard ratio; HVLT-R, Hopkins Verbal Learning Test-Revised; MRI, magnetic resonance imaging; OS, overall survival; PCI, prophylactic cranial irradiation; PI, principal investigator.

arm compared with the high dose arm (29% versus 23%, HR: 0.80, $p = 0.18$).[18]

An ongoing phase 2/3 randomized trial, NRG Oncology CC003 (NCT02635009), is testing the role of hippocampal avoidance in patients undergoing PCI for both limited-stage and ES-SCLC. Hippocampal avoidance is a strategy used to reduce neurocognitive toxicity of brain radiation by using intensity-modulated radiation therapy to pull dose away from the hippocampi. NRG CC003 randomizes patients to PCI alone compared with PCI with hippocampal avoidance. The study is currently accruing in phase 3, with a primary end point of determining whether PCI with hippocampal avoidance reduces the likelihood of neurocognitive deterioration at 6 months from baseline as measured by the Hopkins Verbal Learning Test–Revised delayed recall instrument.

Treatment of Brain Metastases

Whole-brain radiation therapy (WBRT) has been the recommended local therapy for brain metastases owing to the diffuse nature of small-cell brain metastases that generally respond well to low-dose radiation therapy. The standard dose for WBRT is 30 Gy in 10 fractions.[19] Notably, small-cell and other radiosensitive cancer types were excluded from the landmark Radiation Therapy Oncology Group (RTOG) trials that established stereotactic radiosurgery (SRS) as a new standard, which was first developed as a boost after WBRT.[20] Therefore, it should be emphasized that WBRT is the current standard of care for small-cell brain metastases.

In recent years, some institutions have begun to deliver SRS on a case-to-case basis in lieu of WBRT for small-cell brain metastases. A recent retrospective study evaluated SRS versus WBRT in a large cohort of 710 patients between 1994 and 2018. This study reported an improved time to central nervous system progression in patients receiving WBRT (HR: 0.38, 95% confidence interval [CI]: 0.26–0.55, $p < 0.001$), without an improvement in OS (median 6.5 mo for SRS versus 5.2 mo for WBRT $p = 0.003$).[21] Further randomized trials are under development that will test comparing WBRT to SRS in ES-SCLC, and will be of great value in clarifying which patients may benefit from SRS instead of WBRT. Of note, SRS is used as a standard in ES-SCLC for salvage local therapy when brain metastases recur after WBRT.

Consolidative Thoracic Radiation

After first-line systemic therapy, approximately 75% of patients with ES-SCLC have a residual intrathoracic disease, and approximately 90% of patients will progress with intrathoracic disease.[8] Given these high rates of intrathoracic progression and limited efficacy of second-line therapies, thoracic radiation has been studied as a means to improve outcomes for this recalcitrant disease. Four randomized trials have been performed testing the utility of thoracic radiation on disease control and OS.[11,12,22,23]

A single-institution randomized trial performed by Jeremic et al.[22] found an OS benefit to thoracic radiation in patients with complete resolution of extrathoracic disease after first-line systemic therapy and a complete or partial response in local disease. Patients received 54 Gy with concurrent chemotherapy or further chemotherapy alone. The 1-year survival was significantly higher for patients receiving thoracic radiation (65%), and the 5-year survival was 9.1% versus 3.7% ($p = 0.041$) in the no thoracic radiotherapy group.[22] The caveat of this study is that it was a small trial conducted in the 1990s, and it is unclear if the study's findings are broadly generalizable.

RTOG 0937 was a randomized phase 2 trial evaluating thoracic radiotherapy (TRT) and radiation to metastatic sites in patients with oligometastatic ES-SCLC with one to four metastatic sites and no evidence of brain metastases at diagnosis.[12] Patients received 25 Gy PCI and were then randomized to either consolidative radiation (30 to 45 Gy to the thorax and sites of distant disease) or observation. The 1-year OS was not significantly different at 60.1% for the PCI alone arm versus 50.8% for the TRT plus oligometastatic sites plus PCI arm. The first site of failure was significantly different between treatment arms, with progression at sites of presenting disease in 78.1% for the control arm and 41.9% for the experimental arm. Locoregional progression (first site of failure) occurred in 25.8% versus 62.5%, with significantly less locoregional progression in the TRT arm. Grade 3 or higher adverse events attributed to therapy occurred more frequently in the experimental arm compared with the control arm of PCI alone (25% versus 9.5%), with grade 4 toxicities including hematologic and pulmonary toxicity.

The CREST trial is the largest randomized trial evaluating the utility of consolidative thoracic radiation (TRT).[11] This trial randomized 495 patients (exclusion criteria of brain metastases or pleural disease) with any response to chemotherapy to either thoracic radiation, 30 Gy in 10 fractions, or no thoracic radiation, with PCI administered in all patients. The primary end point of improved 1-year OS was not met ($p = 0.066$), but 2-year OS was significantly improved, 13% versus 3% ($p = 0.004$). Isolated thoracic progression was significantly reduced in the TRT arm, at 19.8% compared with 46% in the control arm. The thorax as the first site of disease progression was significantly lower in the TRT arm, at 41.7% compared with 77.8%. TRT was well tolerated with no grade 5 toxicities. Grade 3 and 4 toxicities occurred in approximately 10% of patients, with fatigue being the most common event, with no differences between the treatment arms.

Further analysis of the CREST trial revealed that the survival benefit from TRT was driven by patients with residual disease after systemic therapy.[24] Of note, patients were not stratified a priori for a response to systemic therapy; thus, this finding is hypothesis-generating. Notably, this trial also included PCI if brain MRI is lacking before study enrollment, which is not routine practice in North America. Other important points include the relatively high rates of thoracic failure in the CREST trial patients who received radiation, perhaps indicating that a higher TRT dose may be beneficial. Retrospective and database studies reported improved OS when the TRT dose was 45 Gy or higher,[25,26] also suggesting a benefit to doses higher than those used in the CREST study. A secondary analysis of the CREST trial also revealed that survival was significantly improved in patients with two or fewer extrathoracic sites of disease, suggesting that this patient group be further evaluated for treatment intensification.[27] The pertinent trials studying consolidative thoracic radiation in ES-SCLC are summarized in Table 2.

Regarding radiation treatment volumes for consolidative TRT, both the CREST trial and RTOG 0937 treated postchemotherapy gross disease with appropriate clinical tumor volume and planned tumor volume margins, also including pretreatment hilar and mediastinal nodal stations that were initially involved but may have responded (even completely) to chemotherapy. A single-arm phase 2 study of thoracic radiation in ES-SCLC had nearly 50% rates of locoregional recurrence when the postchemotherapy gross disease was treated with margin without irradiation to previously involved nodal regions.[28]

An NRG oncology trial in ES-SCLC, NRG LU007 (NCT04402788), will randomize patients without progressive disease after four to six cycles of platinum or etoposide or atezolizumab to maintenance atezolizumab versus radiation (up to five sites including primary thoracic disease) plus maintenance atezolizumab. Patients will be stratified by the number of radiated lesions (1–3 versus >3), partial response versus stable disease after first-line systemic therapy, and performance status. This study will enroll 324 patients. PCI is optional. This study will be critical to determining the role of thoracic radiation in the setting of first-line chemoimmunotherapy.

Immunotherapy

The recent U.S. Food and Drug Administration (FDA) approvals of atezolizumab and durvalumab in combination with first-line platinum or etoposide chemotherapy represent the first new therapies to be approved for ES-SCLC in several decades. The following section outlines the key clinical trials leading to the integration of immunotherapy into standard treatment for ES-SCLC.

In the first-line setting, an initial randomized trial of carboplatin or etoposide plus or minus ipilimumab did

Table 2. Studies Evaluating the Role of Consolidative Thoracic Radiation Before the Era of Immunotherapy in ES-SCLC

Reference	Study Type	Patients	Study Objective (Purpose of the Study)	Study Results
1. Slotman et al. 2015[11]	Phase 3	498	To determine whether consolidative thoracic radiation after chemotherapy and PCI improves survival in ES-SCLC	OS at 1 year was not significantly different between groups: 33% (95% CI: 27-39) for the thoracic radiotherapy group versus 28% (95% CI: 22-34) for the control group (HR: 0·84, 95% CI: 0·69-1·01; $p = 0·066$). In a secondary analysis, 2-year OS was 13% (95% CI: 9-19) vs. 3% (95% CI: 2-8; $p = 0·004$).
2. Gore et al. 2017[12]	Phase 2	97	Randomized phase 2 trial evaluating 1-year OS with PCI or PCI+cRT to intrathoracic disease and extracranial metastases for extensive-disease SCLC	The 1-year OS was not different between the groups: 60.1% (95% CI: 41.2-74.7) for PCI and 50.8% (95% CI: 34.0-65.3) for PCI+cRT ($p = 0.21$). The 3- and 12-mo rates of progression were 53.3% and 79.6% for PCI and 14.5% and 75% for PCI+cRT, respectively. Time to progression favored PCI+cRT (HR: 0.53, 95% CI: 0.32-0.87, $p = 0.01$).
3. Jeremic et al. 1999[22]	Phase 2	210	To investigate the efficacy and toxicity of PE, CHT with or without accelerated hyperfractionated radiation therapy and concurrent daily carboplatin or etoposide in ES-SCLC	The radiation arm had significantly better survival rates than the control arm, median survival 17 vs. 11 mo; 5-year survival rate, 9.1% vs. 3.7%, respectively; $p = 0.041$).
4. Narayan et al. 2015[23]	Phase 3	358	To evaluate the efficacy and toxicity of continuum platinum-based chemotherapy vs. chemoradiotherapy in ES-SCLC in Asian Indian patient population	Median PFS: 15 mo (cRT arm) vs. 10 mo (CT only) (HR: 0.78; 95% CI: 0.56-1.18; $p = 0.06$) and 5-year OS 10.3% (cRT arm) vs. 6.2% (CT only) (HR: 0.83; 95% CI: 0.49-1.29; $p = 0.47$) respectively.

CHT, chemotherapy; CI, confidence interval; cRT, consolidative radiation therapy; CT, computed tomography; EC-SCLC, extensive-stage SCLC; HR, hazard ratio; OS, overall survival; PCI, prophylactic cranial irradiation; PE, cisplatin or etoposide; PFS, progression-free survival.

not improve clinical outcomes in previously untreated ES-SCLC.[29] In ES-SCLC, who had received previous platinum therapy, CheckMate-032 was designed as a phase 1/2 trial designed to evaluate response rates of nivolumab and nivolumab plus ipilmumab at varying dose levels, with a primary end point of response rate. In a randomized cohort, response rates with nivolumab alone (3 mg/kg) were 12% and increased to 21% for nivolumab (1 mg/kg) and ipilumumab (3 mg/kg).[30] This led to the FDA approval of nivolumab for the therapy of patients with SCLC in the third-line setting in August 2018.[31]

Most recently, immunotherapy was advanced to frontline therapy of ES-SCLC patients with the IMpower 133 pivotal trial.[4] Patients received standard four cycles of carboplatin with etoposide with or without concurrent and maintenance atezolizumab, an anti–programmed death-ligand 1 (PD-L1) inhibitor antibody. The inclusion criteria included previously untreated patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 without untreated brain metastases. At a median follow-up of 13.9 months, the OS was 12.3 months and 10.3 months in the atezolizumab and placebo group, respectively. This was the first trial over the past several decades, which reported an OS improvement compared with the decades-old platinum-etoposide doublet. PCI was allowed during the maintenance phase, and no additional toxicities from PCI during maintenance therapy with atezolizumab were reported, although data are still premature. This trial did not allow consolidative thoracic radiation, though palliative radiation was allowed.

The CASPIAN trial, an open-label phase 3 randomized trial, also recently found an improvement in OS with a PD-L1 inhibitor, durvalumab, added to first-line platinum or etoposide chemotherapy. This study was similar in design to IMpower 133, but did allow untreated, asymptomatic brain metastases and also allowed carboplatin or cisplatin. Untreated patients were randomized to one of the following three arms: (1) durvalumab plus platinum or etoposide for four cycles followed by durvalumab alone every 4 weeks until disease progression, (2) platinum or etoposide alone for four to six cycles followed by optional PCI, or (3) durvalumab plus tremelimumab plus platinum or etoposide for four cycles followed by durvalumab alone every 4 weeks until disease progression. The median OS was significantly improved for the durvalumab arm—13 months versus 10.3 months. PCI was not allowed in either experimental arm.[3] At the American Society of Clinical Oncology (ASCO) 2020, an updated analysis was presented that included the durvalumab plus tremelimumab arm; this arm did improve OS numerically over platinum or etoposide alone, but did not reach statistical significance (HR: 0.82, 95% CI: 0.68–1.00, $p = 0.0451$). Durvalumab plus platinum or etoposide continued to exhibit an improvement in OS (HR: 0.75, 95% CI: 0.62–0.91, $p = 0.0032$).[32]

Another study, KEYNOTE-604, was a double-blind, phase 3 trial of pembrolizumab plus platinum or etoposide chemotherapy versus placebo plus platinum or etoposide as first-line therapy for ES-SCLC. These results were presented at ASCO 2020, reporting an improvement in the primary end point of progression-free survival (PFS) (HR: 0.75, 95% CI: 0.61–0.91), with a median of 4.5 versus 4.3 months. The co-primary end point of OS was numerically improved (HR: 0.80, 95% CI: 0.64–0.98), median 10.8 versus 9.7 months, but the significance threshold was not met for the intent-to-treat population.[33]

Another randomized phase 2 study of platinum or etoposide in combination with nivolumab was presented at ASCO 2020. This ECOG or ACRIN trial, EA5161, randomized newly diagnosed patients to platinum or etoposide plus nivolumab for four cycles followed by nivolumab maintenance or platinum or etoposide for four cycles followed by observation. PCI was allowed per investigator's discretion. The primary end point of this study was PFS, and PFS was reportedly improved with an HR of 0.65 (95% CI: 0.46–0.91, $p = 0.012$), with a median PFS of 5.5 versus 4.6 months. OS was also improved, with a HR of 0.67 (95% CI: 0.46–0.98, $p = 0.038$).[34]

Another strategy of immunotherapy in the consolidative setting only for previously untreated ES-SCLC has been recently tested in the CheckMate-451 trial. This phase 3 trial randomized patients with at least stable disease after platinum-based chemotherapy, ECOG performance status 0/1, and no evidence of brain metastases to nivolumab, nivolumab plus ipilumumab, or placebo. Survival was not prolonged with nivolumab plus ipilumumab versus placebo (HR: 0.92; 95% CI: 0.75–1.12, $p = 0.3693$) or nivolumab versus placebo (HR: 0.84, 95% CI: 0.69–1.02).[35]

To summarize the recent data on the use of immune checkpoint inhibitors in ES-SCLC, several trials have found a small but consistent OS benefit when PD-L1 or programmed cell death-protein 1 inhibitors are added

Table 3. Pivotal Chemoimmunotherapy Trials in ES-SCLC

Reference	Study Type	Patients	Study Objective (Purpose of Study)	Study Results
1. Horn et al. 2018[4]	Randomized phase 3	403	To determine whether carboplatin + etoposide + atezolizumab improves OS and PFS in first-line therapy in ES-SCLC	OS was 12.3 mo in the atezolizumab group and 10.3 mo in the placebo group (HR: 0.70; 95% CI: 0.54-0.91; $p = 0.007$). The median PFS was 5.2 mo and 4.3 mo, respectively (HR: 0.77; 95% CI: 0.62-0.96; $p = 0.02$).
2. Paz-Ares et al. 2019[3]	Randomized phase 3	537	To assess durvalumab, with or without tremelimumab, in combination with etoposide plus either cisplatin or carboplatin (platinum-etoposide) in treatment-naive patients with ES-SCLC	Durvalumab plus platinum- etoposide was associated with a significant improvement in OS, with an HR: 0·73 (95% CI: 0·59-0·91; $p = 0·0047$]); median OS was 13·0 mo (95% CI: 11·5-14·8) in the durvalumab plus platinum-etoposide group vs. 10·3 mo (9·3-11·2) in the platinum-etoposide group.
3. Rudin et al. 2020[33]	Randomized phase 3	453	To determine whether pembrolizumab + platinum or etoposide improves OS and PFS as first-line therapy in ES-SCLC	Improved PFS (HR: 0.75, [95% CI: 0.61-0.91]), with a median of 4.5 vs. 4.3 mo. The coprimary end point of OS was numerically improved (HR: 0.80, [95% CI: 0.64-0.98]), median 10.8 vs. 9.7 mo, but the significance threshold was not met for the intent-to-treat population.
4. Leal et al. 2020[34]	Randomized phase 2	160	To determine whether platinum or etoposide + nivolumab improves PFS compared with platinum or etoposide alone	PFS was improved with a HR: 0.0.65 (95% CI: 0.46-0.91, $p = 0.012$), with a median PFS of 5.5 vs. 4.6 mo. OS was also improved, with a HR: 0.67 (95% CI: 0.46-0.98, $p = 0.038$).
5. Owonikoko et al. 2019[35]	Randomized phase 3	834	To determine whether OS is improved with nivo + ipi or nivo vs. placebo as maintenance therapy in pts with ED-SCLC who did not progress on first-line platinum-based chemotherapy	OS was not prolonged with nivolumab + ipilumumab vs. placebo (HR: 0.92; 95% CI: 0.75-1.12; $p = 0.3693$) or nivolumab vs. placebo (HR: 0.84, 95% CI: 0.69-1.02).

CI, confidence interval; EC-SCLC, extensive-stage SCLC; HR, hazard ratio; ipi, ipilmumab; nivo, nivolumab OS, overall survival; PFS, progression-free survival; pts, patients.

to platinum or etoposide and continued as maintenance therapy in the first-line treatment of ES-SCLC. This represents a new standard of care for the ES-SCLC population and brings to light the question of how best to incorporate palliative radiation, PCI, and consolidative thoracic radiation into this new treatment paradigm. Table 3 summarizes these findings.

The use of immunotherapy in the maintenance phase raises specific safety questions when palliative radiation therapy is indicated. There are limited safety data regarding radiotherapy during immune checkpoint inhibitor therapy in patients with ES-SCLC, particularly with higher doses such as those used in stereotactic body radiation therapy (SBRT). Palliative radiotherapy was allowed in the IMpower 133 trial without any unexpected safety signals. There are trials underway evaluating the potential synergistic role of radiation with immunotherapy in ES-SCLC, which will provide further safety and efficacy data for radiation in combination with immunotherapy. Notably, a recent single-arm phase 2 trial from MD Anderson reported no worrisome safety signal when combining thoracic radiation with pembrolizumab in ES-SCLC.[36] Building on this concept of radiation and immunotherapy synergy in ES-SCLC, NRG Oncology LU-007 (NCT04402788) will test the utility of consolidative thoracic radiation and SBRT to metastatic sites of disease after four to six cycles of platinum or etoposide or atezolizumab. The clinical trials studying consolidative radiation in the setting of chemoimmunotherapy in ES-SCLC are summarized in Table 4.

Summary of Recommendations

The optimal treatment for ES-SCLC has evolved rapidly, with recent positive randomized trials reporting improvements in outcomes with immunotherapy added to first-line platinum or etoposide chemotherapy. The use of both PCI and thoracic radiation has been reported to improve survival in randomized trials that predate the era of immunotherapy, and have not been consistently incorporated into recent phase 3 clinical trial designs testing chemotherapy and immunotherapy combinations. The role of these treatments remains a little controversial; however, the committee was in agreement that PCI could be given after first-line systemic therapy, or alternatively could be forgone if MRI-based brain surveillance was incorporated into the follow-up care of the patient. For the treatment of brain metastases, whole-brain radiation is felt to be the standard of care by the committee given these patients were excluded from randomized trials testing SRS in patients with brain metastases. However, the committee acknowledges that this is an active area of research, and clinical trials are developing that will test SRS in this patient population.

There is consensus that thoracic radiation should be considered in patients with residual disease after chemotherapy, with a range of doses being appropriate. PCI could be given with thoracic radiation, or not given if with MRI surveillance were carried out. The committee also feels that thoracic radiation should be considered after chemoimmunotherapy in patients with residual disease. Finally, the role of SBRT in the low-volume metastatic disease was also considered by the committee and considered appropriate in selected cases. These results are summarized in Tables 5 to 9.

In summary, the expert panel on radiation oncology strongly recommends the following: (1) either PCI (25 Gy/10 fractions) or MRI surveillance every 3 months is usually appropriate in patients with no evidence of brain metastases who respond to systemic therapy (if PCI is lacking, follow-up without brain surveillance imaging is not appropriate); (2) whole-brain radiation (30 Gy in 10 fractions) is usually appropriate for optimal

Table 4. Completed and Ongoing Trials of Chemoimmunotherapy Followed by Consolidative Thoracic Radiation in ES-SCLC

Reference	Study Type	Patients or Events	Study Objective (Purpose of the Study)	Study Results
1. Welsh et al. 2020[36]	Phase 1	38	Assessment of the safety of combining pembrolizumab with TRT after platinum or etoposide chemotherapy for ES-SCLC	All tolerated pembrolizumab at 100–200 mg with no dose-limiting toxicity in the 35-d window. There were no grade 4–5 toxicities; 2 patients (6%) experienced grade 3 events. Median PFS and OS were 6.1 mo (95% CI: 4.1–8.1) and 8.4 mo (95% CI: 6.7–10.1).
2. NRG Oncology LU-007 (NCT04402788) PI: Nguyen, Q.	Phase 2/3	324	To compare PFS and OS between patients receiving platinum or etoposide or atezolizumab followed by consolidative radiation to the chest and distant sites of disease and maintenance atezolizumab vs. maintenance atezolizumab alone	Trial actively accruing or Results pending.

CI, confidence interval; EC-SCLC, extensive-stage SCLC; OS, overall survival; PI, principal investigator; PFS, progression-free survival; TRT, thoracic radiotherapy.

Table 5. Clinical Condition: ES-SCLC, Variant 1

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	References	SQ	SOE	SOR
Observation without planned additional brain imaging unless the patient becomes symptomatic	U	1	1	6	1			1			3		9 (PMID 17699816)	1	M	↑
PCI to 25 Gy in 10 fractions	A						2	6	2	1	7		9 (PMID 17699816) 15 (PMID 6269769) 16 (PMID 10441603) 17 (PMID 11432756)	1 1 2 2	S	↑
Observation with a brain MRI with gadolinium Q 3 mo	A						1	8	3	1	7		10 (PMID 28343976)	1	S	↑
PCI to 36 Gy in 18 fractions	U	5	1	2		1	1	1			2		18 (PMID 19386548)	1	S	↑

Note: Variant 1: A 65-year-old man with ES-SCLC, with initial staging PET or CT that exhibited polymetastatic disease with bone, liver, and adrenal metastases. Brain MRI with gadolinium was negative for intracranial disease. The patient had a partial response to six cycles of carboplatin or etoposide. Follow-up brain MRI again revealed no evidence of intracranial disease.
Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5. **SQ: Study Quality** (see Appendix Table 1).
Rating: A-Usually appropriate; **M**-May be appropriate; U-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-expert consensus; **EO**-expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation. PMID: PubMed identification number.
CT, computed tomography; EC-SCLC, extensive-stage SCLC; MRI magnetic resonance imaging; PCI, prophylactic cranial irradiation; PET, positron emission tomography

management of brain metastases, whereas SRS remains investigational and may be appropriate in selected patients after discussion of available evidence and the potential for increased risk of distant central nervous system failure (a clearer delineation of the relative risks and benefits of these strategies is pending results of clinical trials utilizing SRS in this patient population); (3) for patients who are not candidates for chemo-immunotherapy, the options of either observation after four to six cycles of platinum or etoposide or thoracic radiation with PCI is usually appropriate (PCI alone or thoracic radiation alone may also be appropriate with

Table 6. Clinical Condition: ES-SCLC, Variant 2

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	References	SQ	SOE	SOR
Whole-brain radiation to 30 Gy/ 10 fractions followed by MRI surveillance every 3 mo	A			1			1	4	5	1	7.5		10 (PMID 28343976)	1	S	↑
Whole-brain radiation to 30 Gy in 10 fractions followed by imaging as clinically indicated	A				1		1	3	1	5	8		9 (PMID 17699816)	1	S	↑
SRS to 21-24 Gy to all three subcentimeter metastases	M		1	2	6	2	2				4				M	↑
Continued observation with no brain specific therapy	U	2	5	2	2						2				M	↑

Note: Variant 2. A 72-year-old man with ES-SCLC, with a 3-cm right upper lobe mass, bulky subcarinal and bilateral paratracheal disease, and bilateral pulmonary nodules. Brain MRI with gadolinium was negative for intracranial disease. The patient had a partial response to six cycles of carboplatin or etoposide. Follow-up brain MRI again revealed no evidence of disease. He did not receive PCI and did not undergo MRI surveillance. After 6 months, he was found to have three subcentimeter brain metastases after being admitted to the hospital with a syncopal episode.
Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5. **SQ: Study Quality** (see Appendix Table 1).
Rating: A-Usually appropriate; **M**-May be appropriate; U-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-expert consensus; **EO**-expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation
EC-SCLC, extensive-stage-SCLC; MRI magnetic resonance imaging; PCI, prophylactic cranial irradiation.

Table 7. Clinical Condition: ES-SCLC, Variant 3

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	References	SQ	SOE	SOR
Observation	U	2	1	5		2					3		2 (PMID 16648503)	1	S	↑
2 more cycles of chemotherapy followed by re-evaluation for local therapy	M				1	8	1	2	1		5		11 (PMID 25230595)	1	M	↑
PCI alone	M		1	2	8	1	1				4		9 (PMID 17699816) 11 (28648948)	1 1	M	↑
PCI + thoracic RT (30 Gy)	A						1	5	4	1	7		11 (PMID 25230595)	1	S	↑
PCI + thoracic RT (40-54 Gy)	M				1	1	3	6	2		5[a]	X	19 (PMID 10561263) 20 (WOS[a]:000370365100264) 22 (PMID 29079309) 23 (PMID 30268474)	1 3 3 3	M	-
Thoracic RT alone (30 Gy)	M			1		3	2	4		1	6		10 (PMID 28343976)	1	M	↑
Thoracic RT alone (40-54Gy)	M				2	1	8	2			6		10 (PMID 28343976)	1	M	↑

Note: Variant 3: A 58-year-old woman with ES-SCLC, with initial staging PET or CT that revealed a right upper lobe primary tumor measuring 4.5 cm along with right hilar, paratracheal, subcarinal, and supraclavicular lymph node involvement. There is a portacaval lymph node with a SUVmax of 6, felt to be likely metastatic. The patient received four cycles of carboplatinum and etoposide chemotherapy (not a candidate for atezolizumab owing to active rheumatoid arthritis), with complete resolution of the portacaval lymph node metastasis and a partial response to therapy in the chest with a resolution of disease in all mediastinal lymph node stations, with a remaining 2-cm right upper lobe mass and a continuously enlarged right hilar lymph node.
Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5. **SQ: Study Quality** (see Appendix Table 1).
Rating: A-Usually appropriate; **M**-May be appropriate; U-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-expert consensus; **EO**-expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation
[a]WOS: Web of Science.
CT, computed tomography; EC-SCLC, extensive-stage SCLC; PCI, prophylactic cranial irradiation; PET, positron emission tomography; RT, radiotherapy.

Table 8. Clinical Condition: ES-SCLC, Variant 4

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	References	SQ	SOE	SOR
No radiation therapy	M		1		10			1			4		4 (PMID 30280641) 10 (PMID 28343976) 12 (28648948)	1 1 1	M	↑
PCI	M		1	1	5	3	2		1		4		4 (PMID 30280641) 9 (17699816)	1 1	M	↑
PCI + thoracic RT (30 Gy)	A						1	6	4		7		11 (PMID 25230595) 29 (PMID 31605794)	1 2	M	↑
PCI + thoracic RT (40-54 Gy)	M				3	5	3	1	1		5		19 (PMID 10561263) 22 (PMID 30268474) 29 (PMID 31605794)	1 3 3	M	↑
Thoracic RT (30 Gy)	M					5	6	1	1		6		29 (PMID 31605794)	2	L	↑
Thoracic RT (30-54 Gy) + SBRT to left adrenal gland	M			1	2	3	2	1			5				L	↑

Note: Variant 4: A 67-year-old woman with ES-SCLC, with initial staging PET or CT that revealed a 5-cm left hilar mass and bilateral paratracheal and hilar lymphadenopathy, along with a 3.5 cm, FDG avid left adrenal metastases. The patient received four cycles of carboplatinum or etoposide or atezolizumab. Restaging CT chest or abdomen exhibited partial response in the chest, with a residual 2 cm hilar mass and a 2-cm left paratracheal lymph node. The left adrenal metastases have decreased in size to 3 cm but remain enlarged. Maintenance atezolizumab is recommended along with:
Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5. **SQ: Study Quality** (see Appendix Table 1).
Rating: A-Usually appropriate; **M**-May be appropriate; U-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-expert consensus; **EO**-expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation
CT, computed tomography; EC-SCLC, extensive-stage SCLC; PCI, prophylactic cranial irradiation; PET, positron emission tomography; RT, radiotherapy; SBRT, stereotactic body radiation therapy.

Table 9. Clinical Condition: ES-SCLC, Variant 5

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	References	SQ	SOE	SOR
Maintenance atezolizumab with radiation only for palliation of symptomatic disease	A			2				8			7		4 (PMID 30280641)	1	S	↑
Thoracic radiation (30 Gy) followed by maintenance atezolizumab	M				2	2	8	1			6		29 (PMID 31605794)	2	L	↑
Thoracic radiation (40–54 Gy) followed by maintenance atezolizumab	M	1	1		3	2	3				4.5		29 (PMID 31605794)	2	EO	↑
Two more cycles of carboplatin or etoposide or atezolizumab followed by maintenance atezolizumab	M		1		4	5	1			2	5		4 (PMID 30280641)	1	M	↑

Note: Variant 5: A 71-year-old woman presented with newly diagnosed ES-SCLC with multiple asymptomatic brain metastases and a large right upper lobe tumor with mass effect on the superior vena cava and right hilar lymphadenopathy. She was diagnosed while inpatient and received her first cycle of platinum or etoposide in the hospital. She received 30 Gy whole-brain radiation after her first cycle of chemotherapy and went on to receive carboplatinum or etoposide or atezolizumab for a total of four cycles. A restaging chest CT before maintenance atezolizumab revealed a residual right upper lobe tumor measuring 3 cm. Disagreement, i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5. **SQ: Study Quality** (see Appendix Table 1).
Rating: A-Usually appropriate; **M**-May be appropriate; U-Usually not appropriate
Strength of Evidence: S-Strong; **M**-Moderate; **L**-Limited; **EC**-expert consensus; **EO**-expert opinion
Strength of Recommendation: ↑ Strong Recommendation; ↓ Weak Recommendation; - Additional considerations do not strengthen or weaken the panel's recommendation
CT, computed tomography; EC-SCLC, extensive-stage SCLC.

optimal thoracic radiation dosing ranging from 30 to 54 Gy); and (4) in patients undergoing first-line chemoimmunotherapy, consolidative thoracic radiation (30–54 Gy) and PCI is usually appropriate; however, the strength of evidence for thoracic radiation and PCI is limited in this setting. In addition, the following may be appropriate: (1) including the use of radiation only for palliation, (2) the use of PCI alone, (3) the use of thoracic radiation without PCI, and (4) SBRT to areas of metastatic disease.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.09.013.

References

1. American Cancer Society. Cancer Facts and Figures 2018. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2018.html. Accessed November 1, 2018.
2. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol*. 2006;24:2038–2043.
3. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2019;394:1929–1939.
4. Horn L, Mansfield AS, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379:2220–2229.
5. Jalal SI, Lavin P, Lo G, Lebel F, Einhorn L. Carboplatin and etoposide with or without palifosfamide in untreated extensive-stage small-cell lung cancer: a multicenter, adaptive, randomized phase III study (MATISSE). *J Clin Oncol*. 2017;35:2619–2623.
6. Spigel DR, Townley PM, Waterhouse DM, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. *J Clin Oncol*. 2011;29:2215–2222.
7. Socinski MA, Smit EF, Lorigan P, et al. Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naive patients with extensive-stage small-cell lung cancer. *J Clin Oncol*. 2009;27:4787–4792.
8. Hurwitz JL, McCoy F, Scullin P, Fennell DA. New advances in the second-line treatment of small cell lung cancer. *Oncologist*. 2009;14:986–994.
9. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med*. 2007;357:664–672.

10. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18:663–671.
11. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial [published correction appears in *Lancet*. 2015;385:28]. *Lancet*. 2015;385:36–42.
12. Gore EM, Hu C, Sun AY, et al. Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extracranial irradiation for extensive-disease small cell lung cancer (ED SCLC): NRG oncology RTOG 0937. *J Thorac Oncol*. 2017;12:1561–1570.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006–1012.
14. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ*. 1995;311:376–380.
15. Eagan RT, Frytak S, Lee RE, Creagan ET, Ingle JN, Nichols WC. A case for preplanned thoracic and prophylactic whole brain radiation therapy in limited small-cell lung cancer. *Cancer Clin Trials*. 1981;4:261–266.
16. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med*. 1999;341:476–484.
17. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer*. 2001;1:5.
18. Le Pechoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol*. 2009;10:467–474.
19. Tsao MN, Xu W, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev*. 2018;1:CD003869.
20. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet*. 2004;363:1665–1672.
21. Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of first-line radiosurgery vs whole-brain radiotherapy for small cell lung cancer brain metastases: the FIRE-SCLC cohort study [published correction appears in https://doi.org/10.1001/jamaoncol.2020.3404]. *JAMA Oncol*. 2020;6:1028–1037.
22. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. *J Clin Oncol*. 1999;17:2092–2099.
23. Narayan S, et al. A prospective randomized phase III Study of continuum chemotherapy versus chemo-radiotherapy in ES-SCLC in Asian Indian. *J Thorac Oncol*. 2015;10(suppl 2):S193–S193.
24. Slotman B, Faivre-Finn C, Tinteren HV, et al. Which patients with ES-SCLC should receive thoracic radiotherapy (TRT) routinely? *J Thorac Oncol*. 2015;10(suppl 2): S193–S193.
25. Xu LM, Zhao LJ, Simone CB 2nd, et al. Receipt of thoracic radiation therapy and radiotherapy dose are correlated with outcomes in a retrospective study of three hundred and six patients with extensive stage small-cell lung cancer. *Radiother Oncol*. 2017;125:331–337.
26. Hasan S, Renz P, Turrisi A, Colonias A, Finley G, Wegner RE. Dose escalation and associated predictors of survival with consolidative thoracic radiotherapy in extensive stage small cell lung cancer (SCLC): a National Cancer Database (NCDB) propensity-matched analysis. *Lung Cancer*. 2018;124:283–290.
27. Slotman BJ, Faivre-Finn C, van Tinteren H, et al. Which patients with ES-SCLC are most likely to benefit from more aggressive radiotherapy: a secondary analysis of the phase III CREST trial. *Lung Cancer*. 2017;108:150–153.
28. Yee D, Butts C, Reiman A, et al. Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small cell lung cancer. *Radiother Oncol*. 2012;102:234–238.
29. Reck M, Luft A, Szczesna A, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer [published correction appears in *J Clin Oncol*. 2019;37:3327]. *J Clin Oncol*. 2016;34:3740–3748.
30. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17:883–895.
31. Ready N, Farago AF, de Braud F, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. *J Thorac Oncol*. 2019;14:237–244.
32. Paz-Ares LG, Dvorkin M, Chen Y, et al. Durvalumab±tremelimumab+ platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): updated results from the phase III CASPIAN study. *J Clin Oncol*. 2020;38(suppl 15): 9002–9002.
33. Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. *J Clin Oncol*. 2020;38:2369–2379.
34. Leal T, Wang Y, Dowlati A, et al. Randomized phase II clinical trial of cisplatin/carboplatin and etoposide (CE) alone or in combination with nivolumab as frontline therapy for extensive-stage small cell lung cancer (ES-SCLC): ECOG-ACRIN EA5161. *J Clin Oncol*. 2020;38(suppl 15):9000–9000.
35. Owonikoko TK, Kim HR, Gonindan R, et al. Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): results from the double-blind, randomized phase III CheckMate 451 study. *Ann Oncol*. 2019;30:ii77.
36. Welsh JW, Heymach JV, Chen D, et al. Phase I trial of pembrolizumab and radiation therapy after induction chemotherapy for extensive-stage small cell lung cancer. *J Thorac Oncol*. 2020;15:266–273.