American Radium Society™
Appropriate Use Criteria
on Radiation Therapy for Extensive-stage Small Cell Lung Cancer


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Conflicts of Interest Disclosure Statement:

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society™ in perpetuity.

The ARS Appropriate Use Criteria Steering Committee reviewed these disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work.

Disclosures potentially relevant to the content of this guideline are provided.

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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 based on National Library of Medicine® Medical Subject Headings (MeSH®) with addition of subject-specific keywords. Due to the broad scope of medical literature on extensive-stage small cell lung cancer, the expert panel composed of multidisciplinary radiation, medical, and surgical oncologists as well as 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
Abstract

Background: Standard of care therapy for Extensive-stage small cell lung cancer (ES-SCLC) has recently changed with the results of two large, randomized trials demonstrating improved survival with the addition of immunotherapy to first-line platinum/etoposide chemotherapy. This has led to uncertainty regarding consolidative thoracic radiation as well as prophylactic cranial irradiation (PCI) after initial chemo-immunotherapy.

Methods: The American Radium Society (ARS) 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 application of consensus methodology (modified Delphi) to rate the appropriateness of treatments recommended by the panel for ES-SCLC.

Conclusions: Current evidence supports initial chemo-immunotherapy for extensive small cell lung cancer as well as either PCI or surveillance with magnetic resonance imaging (MRI) every 3 months for optimal management of the brain. Patients with brain metastases should receive whole brain radiation, 30 Gy in 10 fractions. While there is limited evidence, consolidative thoracic radiation after chemo-immunotherapy can be considered with the recommended doses ranging from 30-54 Gy.

Introduction

Small cell lung cancer comprises 13% of all lung cancers, and the majority are diagnosed at an advanced, extensive stage [1]. The cornerstone of treatment for extensive stage small cell lung cancer (ES-SCLC) has been 4-6 cycles of platinum/etoposide chemotherapy, with median survival ranging from 6-12 months [2]. Although response rates to first-line systemic therapy for
ES-SCLC have typically been robust, progression of disease after initial response to systemic therapy was nearly uniform and commonly occurred within 6 months. Relatively early progression and response rates to second line therapies of less than 10%6] resulted in poor long-term clinical outcomes [3-5].

A recent advance demonstrated a modest improvement in median overall survival with the addition of immunotherapy to systemic therapy in the first-line setting [6, 7]. But the advance in systemic therapy made the role of consolidative thoracic radiation even more unclear. Prior to the incorporation of immunochemotherapy, thoracic radiation improved 2 year OS in the CREST study [8], but another randomized trial failed to show a survival benefit to consolidative thoracic radiation [9].

In one large randomized trial, prophylactic cranial irradiation (PCI) has been shown to improve overall survival (OS) in patients with at least a partial response to systemic therapy [10]; however, a separate randomized trial in which brain magnetic resonance imaging (MRI) was repeated after chemotherapy and during follow-up showed no benefit to PCI [11]. One implication is that for patients who are regularly imaged with MRI, early “salvage” brain radiation can catch those patients who need it.

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.
Materials and Methods

A literature review was conducted on peer-reviewed journals using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The PubMed database was queried to retrieve all pertinent articles that included key words including: extensive stage small cell lung cancer, prophylactic cranial irradiation, and consolidative thoracic radiation using no date restrictions and including all articles through November 2019. 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 [13] (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.

Immunotherapy

Clinical introduction of immune checkpoint inhibitors has revolutionized anticancer therapy for solid tumors. Immunotherapy has been evaluated in ES-SCLC, and currently nivolumab and atezolizumab are FDA approved with first-line platinum/etoposide chemotherapy as well as for the third-line treatment of ES-SCLC. The following section outlines the key clinical trials leading to integration of immunotherapy into standard treatment for ES-SCLC.

Immunotherapy was first introduced in a salvage role, which is particularly appropriate for ES-SCLC since, as mentioned, second line chemotherapy has response rates of less than 10%. In ES-SCLC who had received prior platinum therapy, Checkmate 032 was designed as a
phase I/II trial designed to evaluate response rates of nivolumab and nivolumab plus ipilimumab at varying dose levels, with a primary endpoint 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 ipilimumab (3 mg/kg) [14]. This led to FDA approval of nivolumab for the therapy of SCLC patients in the third-line setting in August of 2018 [15].

Keynote 158 was a single-arm phase II study of previously treated ES-SCLC. Patients received pembrolizumab 200 mg every three weeks for up to 2 years. The primary endpoint was response rate, which was 18.7%. Median PFS was 2 months and median OS was 8.7 months (SITE ASCO 2018 abstract). Pembrolizumab is not currently FDA approved for treatment of ES-SCLC but is included in NCCN guidelines as a treatment option after first-line systemic therapy.

Most recently, immunotherapy was advanced to the front-line therapy of ES-SCLC patients with the IMpower133 pivotal trial [7]. Patients received standard 4 cycles of carboplatin with etoposide with or without concurrent and maintenance atezolizumab, an anti-PD-L1 inhibitor antibody. Inclusion criteria included previously untreated patients with ECOG PS 0 or 1, without untreated brain metastases. At a median follow-up of 13.9 months, the overall survival 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 demonstrated an OS improvement compared to decades old platinum-etoposide doublet. Prophylactic cranial irradiation was allowed during maintenance phase, and no additional toxicities from PCI during maintenance therapy with atezolizumab were reported, although data are still premature. This
The Caspian trial, an open label phase III randomized trial, also recently showed in improvement in OS with a PD-L1 inhibitor, durvalumab, added to first line platinum/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 1 or 3 arms; durvalumab + platinum/etoposide for 4 cycles followed by durvalumab alone every 4 weeks until disease progression, platinum/etoposide alone for 4-6 cycles followed by optional PCI, or durvalumab + tremelimumab + platinum/etoposide for 4 cycles followed by durvalumab alone every 4 weeks until disease progression. Median OS was significantly improved for the durvalumab arm, 13 months vs. 10.3 months. PCI was not allowed in either experimental arm.

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 III trial randomized patients with at least stable disease following platinum-based chemotherapy, PS 0/1, and no evidence of brain metastases to nivolumab, nivolumab plus ipilimumab, or placebo. This study did not reach its primary endpoints of OS and PFS.

Use of immunotherapy in the maintenance phase raises specific safety issues 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. A recent single arm phase II trial from MD Anderson showed no worrisome safety signals when combining thoracic radiation with pembrolizumab in ES-SCLC [16]. Larger studies, however, are needed to definitely show safety and efficacy of consolidative thoracic radiation with the new standard of care backbone of platinum/etoposide + immunotherapy.

**Prophylactic Cranial Irradiation**

Prophylactic cranial irradiation (PCI) has been used as a means of preventing brain metastases in both limited stage and ES-SCLC for several decades due to the underlying assumption of poor penetrance of chemotherapy across the blood brain barrier. Prior reports indicated a 60-70% risk of development of brain metastases following chemotherapy in patients who do not receive PCI[17]. Two meta-analyses have studied the role of PCI in limited stage and ES-SCLC, with both showing a reduction the incidence of brain metastases and an improvement in overall survival [18, 19]. The Auperin meta-analysis demonstrated 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 were conducted in the 1960s-1990s, with included patients receiving a variety of imaging modalities including computerized tomography (CT), scintigraphy, or no imaging. Magnetic resonance imaging (MRI), the current gold standard to detect brain metastases was not typically performed during this era. The applicability of these studies to current clinical practice is questioned given the standard practice now to obtain MRI for a complete staging work-up, 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 EORTC [10] and Japanese [11] studies, which demonstrated conflicting results. The EORTC study, published in 2011, randomized patients with any response to chemotherapy to receive PCI to 20-30 Gy delivered in 4-12 fractions versus observation. Patients underwent brain imaging (CT or MRI) after chemotherapy only if neurologic symptoms were present prior to PCI and in follow-up (to include symptoms of increased intracranial pressure, headache, nausea/vomiting, seizures or focal neurologic symptoms). Findings included statistically significant improvements in 1 year survival in the PCI group (27.1% vs. 13.3%), as well as a significant reduction in the cumulative risk of brain metastases within 1 year (14.6% vs. 40.4%)[10].

The more 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 PCI to 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. Sixty-nine percent 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 to observation (15% vs. 46.2%, 32.9% vs. 59%, and 40.1% vs. 63.8%, respectively). However, overall survival at 1 year was 48.4% in the PCI group and 53.6% in the observation group;
median survival for PCI was 11.6 months compared with 13.7 months in the observation arm (HR 1.27, p = 0.094)[11].

The above studies demonstrated two significant findings: PCI improved survival in a patient population that did not undergo routine MRI surveillance to detect brain metastases, and PCI did not significantly improve survival in patients who underwent frequent brain MRI surveillance and received timely salvage radiation. A SWOG study will further evaluate the concept of close MRI surveillance in lieu of PCI in both limited stage and ES-SCLC in a North American population.

When PCI is delivered, 25 Gy was recommended per the results of EORTC 22003-08004, which tested standard dose (25 Gy in 10 fractions) compared with high dose (36 Gy, delivered in 18-24 fractions) PCI in patients with limited stage small cell lung cancer. No significant increase in brain metastases at 2 years was observed in the standard dose arm compared with the high dose arm (29% vs. 23%, HR .80, p = 0.18)[20].

An ongoing phase II/III randomized trial, NRG Oncology CC003, is testing the role of hippocampal avoidance in patients undergoing PCI for both limited stage and ES-SCLC. This study randomizes patients to PCI alone compared with PCI with hippocampal avoidance. The study is currently accruing in phase III, with a primary endpoint of determining whether PCI with hippocampal avoidance reduces the likelihood of neurocognitive deterioration at 6 months from baseline as measured by the HVLT-R delayed recall instrument.
Consolidative Thoracic Radiation

Following first-line systemic therapy without concurrent immunotherapy, approximately 75% of ES-SCLC patients have residual intra-thoracic disease, and approximately 90% of patients will progress with intrathoracic disease [21]. Given these high rates on intra-thoracic progression and limited efficacy of second-line therapies, thoracic radiation has been studied as a means to improve outcomes for patients with recalcitrant disease.

Four randomized trials have been performed testing the utility of thoracic radiation on disease control and overall survival [8, 9, 22, 23].

A single institution randomized trial performed by Jeremic et al showed an overall survival benefit to thoracic radiation in patients treated with initial chemotherapy who enjoyed a complete resolution of extra-thoracic disease, and a complete or partial response in local disease. After initial chemotherapy and restaging, patients received 54 Gy with concurrent chemotherapy or further chemotherapy alone. One-year survival was significantly higher for patients receiving thoracic radiation (65%) and the 5-year survival was 9.1% vs. 3.7% (p=0.041) in the no thoracic radiotherapy group[22].

RTOG 0937 was a randomized phase II trial evaluating TRT as well as radiation to metastatic sites in patients with oligometastatic ES-SCLC with 1-4 metastatic sites and no evidence of brain metastases at diagnosis [9]. Patients received 25 Gy PCI and the randomization was 30-45 Gy to the thorax and sites of distant disease or no thoracic, or non-CNS radiation. One-year OS was not significantly different, at 60.1% for the PCI alone arm vs. 50.8% for the TRT + oligometastatic sites + PCI arm. 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. Local regional progression (first site of failure) occurred in 25.8% vs. 62.5%, with significantly less local regional 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% vs. 9.5%, with grade 4 toxicities including hematologic and pulmonary toxicity. There was one death related to protocol treatment secondary to radiation pneumonitis in a patient with a V20 higher than allowed per protocol.

The CREST trial is the largest randomized trial evaluating the utility of consolidative thoracic radiation (TRT) [8]. This trial randomized 495 patients (exclusion criteria of brain metastases or pleural disease) who had a response to chemotherapy to either thoracic radiation, 30 Gy in 10 fractions, or no thoracic radiation. PCI was administered in all patients. The primary endpoint of improved 1-year OS was not met (p=0.066), but 2-year OS was significantly improved, 13% vs. 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 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 showed that the survival benefit from TRT was driven by patients with residual disease following systemic therapy [24]. Other important points include the relatively high rates of thoracic failure in the CREST trial, perhaps indicating that a
higher TRT dose may be beneficial. Retrospective studies have suggested 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 showed that survival was significantly improved in patients with 2 or fewer extra-thoracic sites of disease, suggesting that this patient group be further evaluated for treatment intensification[27].

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

A NRG Oncology trial in ES-SCLC (NRG RAPTOR TRIAL, Randomized Phase II/III Trial of consolidation Radiation + Immunotherapy for ES-SCLC) will randomize patients without progressive disease after 4-6 cycles of platinum/etoposide/atezolizumab to maintenance atezolizumab versus radiation (up to 5 sites) plus maintenance atezolizumab. Patients will be stratified by the number of radiated lesions (1-3 vs. > 3), partial response vs. stable disease after first-line systemic therapy, and performance status. This study will enroll 324 patients. PCI is optional.
Summary of Recommendations

Optimal treatment for ES-SCLC has evolved rapidly, with recent positive randomized trials showing improvements in outcomes with immunotherapy added to first line platinum/etoposide chemotherapy. The use of both PCI and thoracic radiation has been shown to improve survival in randomized trials that pre-date the era of immunotherapy, and have not been consistently incorporated into recent phase III clinical trial designs testing chemotherapy and immunotherapy combinations. The role of these treatments remains somewhat controversial, however, the committee was in agreement that PCI could be given after first-line systemic therapy, or alternatively could be forgone if MR-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 stereotactic radiosurgery 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 also no PCI with MRI surveillance. The committee also feels that thoracic radiation should be considered after chemo-immunotherapy in patients with residual disease. Lastly, the role of SBRT to low-volume metastatic disease was also considered by the committee and considered appropriate in select cases.

In Summary, the Expert panel on Radiation Oncology recommends:
• The panel strongly recommends first-line chemoimmunotherapy. The role of consolidative thoracic radiation is unclear, but currently undergoing investigation. Likewise, the use of radiation after chemoimmunotherapy to non-CNS sites of metastases, may be considered,

• The panel recommends strongly that 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. The panel strongly recommends that in the absence of PCI, follow-up without brain surveillance imaging is not appropriate.

• The panel recommends strongly that whole brain radiation (30 Gy in 10 fractions) is usually appropriate for optimal management of brain metastases. Stereotactic radiosurgery remains investigational and may be appropriate pending results of clinical trials utilizing SRS in this patient population.

• For patients who are not candidates for chemoimmunotherapy, the panel strongly recommends that either observation following 4-6 cycles platinum/etoposide is usually appropriate or thoracic radiation with PCI. In addition, PCI alone or thoracic radiation alone may be appropriate, with optimal thoracic radiation dosing ranging from 30-54 Gy.

**Summary of Evidence**

Of the 29 references cited, there were 10 well designed studies, 3 moderately well designed studies, 3 studies with design limitations, 2 meta-analyses, and 13 studies that were not classified as primary references. These references were published between 1981 and 2019.
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 specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding 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 FDA have not been considered in developing these criteria; however, 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 light of all the circumstances presented in an individual examination.
**Clinical Condition:** Extensive Stage Small Cell Lung Cancer

**Variant 1:** 65-year-old male with ES-SCLC, with initial staging PET/CT that shows poly-metastatic disease with bone, liver and adrenal metastases. Brain MRI with gadolinium is negative for intracranial disease. The patient has a partial response to 6 cycles of carboplatin/etoposide. Follow up brain MRI again shows no evidence of intracranial disease.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
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<tbody>
<tr>
<td>Observation without planned additional brain imaging unless the patient becomes symptomatic</td>
<td>U</td>
<td>1 1 6 1 1</td>
<td>3</td>
<td></td>
<td>9 (17699816)</td>
<td>1</td>
<td>M</td>
<td>↑</td>
</tr>
<tr>
<td>PCI to 25 Gy in 10 fractions</td>
<td>A</td>
<td>2 6 2 1 7</td>
<td></td>
<td>9 (17699816)</td>
<td>1 15 (6269769)</td>
<td>1</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>Observation with brain MRI with gadolinium Q 3 months</td>
<td>A</td>
<td>1 8 3 1 7</td>
<td></td>
<td>10 (28343976)</td>
<td>1 17 (11432756)</td>
<td>2</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>PCI to 36 Gy in 18 fractions</td>
<td>U</td>
<td>5 1 2 1 1 1</td>
<td>2</td>
<td>18 (19386548)</td>
<td>1</td>
<td>S</td>
<td>↑</td>
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</table>

**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate
* 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.

**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
**Clinical Condition:** Extensive Stage Small Cell Lung Cancer

**Variant 2:** 72-year-old male 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 is negative for intracranial disease. The patient has a partial response to 6 cycles of carboplatin/etoposide. Follow up brain MRI again shows no evidence of disease. He does not receive PCI and does not undergo MRI surveillance. Six months later, he is found to have 3 subcentimeter brain metastases after being admitted to the hospital with a syncopal episode.

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

**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* 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.

**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.
**Clinical Condition:** Extensive Stage Small Cell Lung Cancer

**Variant 3:** 58-year-old female with ES-SCLC, with initial staging PET/CT that shows a right upper lobe primary tumor measuring 4.5 cm along with right hilar, paratracheal, subcarinal, and supraclavicular lymph node involvement. There is a porta-caval lymph node with a SUV max of 6, felt to be likely metastatic. The patient receives 4 cycles of carboplatinum and etoposide chemotherapy (not a candidate for atezolizumab due to active rheumatoid arthritis), with complete resolution of the porta-caval lymph node, and a partial response to therapy in the chest with resolution of disease in all mediastinal lymph node stations, with a remaining 2 cm right upper lobe mass and a continued enlarged right hilar lymph node.

<table>
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<tr>
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<td>Observation</td>
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<td>2 1 5</td>
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<td></td>
<td>2 (16648503)</td>
<td>1</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>2 more cycles of chemotherapy followed by re-evaluation for local therapy</td>
<td>M</td>
<td>1 8 1 2 1</td>
<td>5</td>
<td></td>
<td>11 (25230595)</td>
<td>1</td>
<td>M</td>
<td>↑</td>
</tr>
<tr>
<td>PCI alone</td>
<td>M</td>
<td>1 2 8 1 1</td>
<td>4</td>
<td></td>
<td>9 (17699816) 11 (28648948)</td>
<td>1</td>
<td>M</td>
<td>↑</td>
</tr>
<tr>
<td>PCI + thoracic RT (30 Gy)</td>
<td>A</td>
<td>1 5 4 1</td>
<td>7</td>
<td></td>
<td>11 (25230595)</td>
<td>1</td>
<td>S</td>
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<tr>
<td>PCI + thoracic RT (40-54 Gy)</td>
<td>M</td>
<td>1 1 3 6 2</td>
<td>5*</td>
<td>X</td>
<td>19 (10561263) 20 (WOS:000370365100264) 22 (29079309) 23 (30268474)</td>
<td>1</td>
<td>M</td>
<td>-</td>
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<tr>
<td>Thoracic RT alone (30 Gy)</td>
<td>M</td>
<td>1 3 2 4</td>
<td>1 6</td>
<td></td>
<td>10 (28343976)</td>
<td>1</td>
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<td>↑</td>
</tr>
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<td>Thoracic RT alone (40-54Gy)</td>
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<td>6</td>
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<td>10 (28343976)</td>
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<td>↑</td>
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**Rating:** A-Usually appropriate; M-May be appropriate; U-Usually not appropriate

* 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.

**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
**Clinical Condition:** Extensive Stage Small Cell Lung Cancer

**Variant 4:** 67-year-old female with ES-SCLC, with initial staging PET/CT that shows 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 receives 4 cycles of carboplatinum/etoposide/atezolizumab. Restaging CT chest/abdomen demonstrates partial response in the chest, with a residual 2cm hilar mass and a 2 cm left paratracheal lymph node. The left adrenal metastases has decreased in size to 3cm but remains enlarged. Maintenance atezolizumab is recommended along with:

<table>
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<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>References</th>
<th>SQ</th>
<th>SOE</th>
<th>SOR</th>
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<td>PCI</td>
<td>M</td>
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<tr>
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<td></td>
<td>7</td>
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<td></td>
<td>5</td>
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<td>M</td>
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<td>6</td>
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<tr>
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<td></td>
<td>L</td>
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</table>

**Rating:** A—Usually appropriate; M—May be appropriate; U—Usually not appropriate

*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.

**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.
Clinical Condition: Extensive Stage Small Cell Lung Cancer

Variant 5: 71-year-old female 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 an inpatient and received her first cycle of platinum/etoposide in the hospital. She received 30 Gy whole brain radiation following her first cycle of chemotherapy and went on to receive carboplatinum/etoposide/tezolizumab for a total of 4 cycles. Restaging CT chest prior to maintenance atezolizumab shows a residual right upper lobe tumor measuring 3 cm.
References