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ORIGINAL ARTICLE

# American Radium Society Appropriate Use Criteria: Radiation Therapy for Limited-Stage SCLC 2020

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## ABSTRACT

**Introduction:** Combined modality therapy with concurrent chemotherapy and radiation has long been the standard of care for limited-stage SCLC (LS-SCLC). However, there is controversy over best combined modality practices for LS-SCLC. To address these controversies, the American Radium Society (ARS) Thoracic Appropriate Use Criteria (AUC) Committee have developed updated consensus guidelines for the treatment of LS-SCLC.

**Methods:** The ARS AUC are evidence-based guidelines for specific clinical conditions that are reviewed by a

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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 LS-SCLC. Agreement or consensus was defined as less than or equal to 3 rating points from the panel median. The consensus ratings and recommendations were then vetted by the ARS Executive Committee and subject to public comment before finalization.

**Results:** The ARS Thoracic AUC committee developed multiple consensus recommendations for LS-SCLC. There was strong consensus that patients with unresectable LS-SCLC should receive concurrent chemotherapy with radiation delivered either once or twice daily. For medically inoperable T1-T2N0 LS-SCLC, either concurrent chemoradiation or stereotactic body radiation followed by adjuvant chemotherapy is a reasonable treatment option. The panel continues to recommend whole-brain prophylactic cranial irradiation after response to chemoradiation for LS-SCLC. There was panel agreement that prophylactic cranial irradiation with hippocampal avoidance and programmed cell death protein-1/programmed death-ligand 1–directed immune therapy should not be routinely administered outside the context of clinical trials at this time.

**Conclusions:** The ARS Thoracic AUC Committee provide consensus recommendations for LS-SCLC that aim to provide a groundwork for multidisciplinary care and clinical trials.



*Keywords:* ARS; AUC; Limited-stage SCLC; Lung cancer

## Introduction

SCLC is the second most common thoracic malignancy, representing 10% to 20% of newly diagnosed lung cancers. Roughly one-third of the cases present in the limited stage (LS) that is potentially amenable to curative local therapy.[1] Historically, the Veterans Affairs Lung Study Group defined LS-SCLC as a tumor burden confined to a hemithorax that could be safely encompassed in a two-dimensional radiation field, whereas the International Association for the Study of Lung Cancer (IASLC) more recently defined LS-SCLC as nonmetastatic disease.[2] Although the American Joint Committee on Cancer and IASLC currently endorse a TNM-staging system for SCLC,[3] the vast majority of clinical trials and evidence-based guidelines have used the LS paradigm to classify patients for eligibility.

Concurrent chemotherapy with early thoracic radiotherapy (TRT) followed by prophylactic cranial irradiation (PCI) is considered to be the standard of care for LS-SCLC. However, recent prospective trials have assessed traditional radiation therapy practices in LS-SCLC, such as the necessity for twice-daily radiation, elective mediastinal irradiation, and PCI. In light of these recent trial findings, the American Radium Society (ARS) reviews the best evidence-based practice for LS-SCLC.

## Materials and Methods

The ARS Appropriate Use Criteria (AUC) Executive Steering Committee selected 15 members for this ARS Thoracic AUC multidisciplinary expert panel composed of radiation, medical, and surgical oncologists with subject matter expertise. An analysis of the medical literature from peer-reviewed journals of the PubMed database from 1970 to 2019 was conducted 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 addition of subject-specific keywords. Owing to the broad scope of medical literature on LS-SCLC, the thoracic AUC expert panel reviewed pertinent studies and excluded those that were not relevant or determined of lower impact or quality. The literature was reviewed and rated by the multidisciplinary panel for quality of study design, cohort size, selection bias, evaluation of participants in relation to time from exposure, and methods of assessments in accordance to the ARS criteria (Supplementary Appendix). Clinical variants were then developed through consensus conference calls to address key practice paradigms and controversies in management. A well-established methodology (modified Delphi) was used by the expert panel to rate the appropriate use of procedures pertaining to the clinical variants through three rounds of anonymous voting with monthly conference calls to discuss rationale to reach consensus. At least 50% attendance was required for conference call quorum to rate the evidence and review anonymous voting. Using panel consensus findings, an evidence-based AUC consensus document was generated and approved by the expert panel. Panel agreement/consensus was defined as ratings falling less than or equal to 3 points from the group median whereas disagreement was defined for any group ratings falling greater than 3 points from the group median. The document was then vetted by the ARS AUC Executive Steering Committee and returned to the panel with reviewer comments for modification. The AUC document was then subject to a 2-week public comment period before finalization. Full details on the ARS AUC methodology and other supporting documents are available at http://www.americanradiumsociety.org/page/aucmethodology.

## Results

### *Early Stage SCLC (T1-T2N0)*

**Resected T1-T2N0 SCLC.** With implementation of low-dose screening chest computed tomography (CT) scans in patients at high risk for developing lung cancer, the identification of early stage (T1-T2N0) SCLC amenable to surgical resection is likely to become more common (Table 1). A large retrospective registry in Japan has revealed 60% to 70% 5-year overall survival for stage I SCLC.[4] With oncologic resection that includes lobectomy and adequate mediastinal nodal sampling, there was panel consensus that adjuvant chemotherapy is recommended to reduce the risk of locoregional and distant progression and has been evaluated in a single-arm phase 2 clinical trial, albeit this was not a strong recommendation given limited strength of evidence.[5] The panel strongly felt that adjuvant TRT is usually not appropriate on the basis of expert consensus unless there is strong concern for residual disease such as in cases of close/positive surgical margin or mediastinal nodal metastases.

The panel evaluated the use of PCI in patients with early stage LS-SCLC who have underwent surgical resection followed by adjuvant chemotherapy, but felt that PCI is controversial, with little prospective evidence to guide practice.[6,7] The panel recognized that although multiple clinical trials and a meta-analysis have revealed a reduction in brain metastases and improvement of survival with PCI,[8] these studies included mostly bulky unresectable disease without brain magnetic resonance imaging (MRI) screening, and it is unclear whether these findings can be extrapolated to surgically resected T1-T2N0 SCLC, a population that has a lower rate of brain metastases compared with more patients with advanced SCLC. In this population, there are small retrospective analyses and pattern of failure analysis of Japan Clinical Oncology Group 9101 suggesting the brain metastasis rate is roughly 15% to 25%.[5,9-11] Furthermore, a National Cancer Database analysis revealed a possible survival benefit associated with PCI in early stage SCLC.[12] For these reasons, the panel provided a weak recommendation owing to sparse evidence. One circumstance in which the panel felt PCI might be considered more strongly is in patients at risk for being lost to follow-up.

**Definitive Radiation Therapy for Early Stage T1-T2N0 SCLC.** In patients with early stage SCLC with high operative risk or who refuse surgery (Table 2), definitive chemoradiation or stereotactic body radiotherapy (SBRT) was evaluated by the committee for appropriateness. There was strong panel consensus that concurrent chemoradiation is usually appropriate because of the inclusion of early stage disease in the CONVERT (concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer) trial. In the CONVERT trial, 16.9% of the patients had stage I to II disease, and those patients had a median survival of 50 months and 5-year local progression free survival of 47% when treated with concurrent chemoradiation.[13] Thus, because patients with T1-T2N0 SCLC were well represented in the randomized CONVERT trial, the panel rated this as strong evidence to support chemoradiation.

The panel evaluated SBRT that has also emerged as a potential treatment option for T1-T2 SCLC, as ablative doses of radiation are expected to have high in-field tumor control rates.[14] Particularly for patients with medically inoperable cT1-T2N0 SCLC, SBRT can be considered if positron emission tomography (PET) scan, brain MRI, and mediastinal staging confirm true early stage disease. A retrospective multi-institutional analysis revealed that patients who received consolidative

**Table 1.** Variant 1

| Procedure | Rating Category | Final Tabulations 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Group Median Rating | Disagree[a] | Reference | SQ | SOE | SOR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adjuvant mediastinal radiation therapy | U | 3 | 3 | 2 | | | | 1 | | | 2 | | N/A | N/A | EC | ↑ |
| Adjuvant cytotoxic chemotherapy | A | 1 | | | | | | 1 | 4 | 3 | 8 | | 4, 5, 11 | 3, 2, 3 | L | – |
| PCI | M | | | | 4 | 2 | 7 | | | | 6 | | 6, 9, 10 | 4, 3, 3 | L | – |
| Adjuvant anti-PD-L1-directed immune therapy | U | 2 | 3 | 3 | | 1 | | | | | 2 | | N/A | N/A | L | ↓ |

*Note:* A 60-year-old woman underwent right upper lobectomy with mediastinal nodal dissection revealing a 2 cm SCLC with negative surgical margins. None of the 15 mediastinal lymph nodes sampled revealed evidence of tumor involvement. SOR: ↑ strong recommendation; ↓ weak recommendation; – additional considerations do not strengthen or weaken the panel's recommendation.

[a]Disagreement, that is, 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.

A, usually appropriate; EC, expert consensus; L, limited; M, may be appropriate; N/A, not applicable; PCI, prophylactic cranial irradiation; PD-L1, programmed death-ligand 1; SOE, strength of evidence; SOR, strength of recommendation; SQ, study quality; U, usually not appropriate.

**Table 2.** Variant 2

| Procedure | Rating Category | Final Tabulations 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Group Median Rating | Disagree[a] | Reference | SQ | SOE | SOR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Concurrent thoracic radiation with platinum/etoposide alone | A | | | | | | | 5 | 3 | 1 | 7 | | 13, 37 | 2, 1 | S | ↑ |
| Definitive SBRT alone | M | | | 4 | 6 | 2 | | 1 | | | 5 | X | 14, 15 | 3, 3 | L | — |
| SBRT followed by consolidative platinum/etoposide | A | | | | | | 1 | 11 | 1 | | 7 | | 14, 15 | 3, 3 | L | — |
| PCI after chest-directed therapy and chemotherapy | M | 1 | | | 2 | 2 | 8 | | | | 6 | | 8 | 1 | EO | — |
| Consolidative anti-PD-L1-directed immune therapy after chest-directed therapy | U | 2 | 2 | 4 | | 1 | | | | | 3 | | N/A | N/A | L | ↓ |

*Note:* A 75-year-old man with severe chronic obstructive pulmonary disease is found to have a 1.5 cm right upper lobe SCLC without evidence of mediastinal or hilar adenopathy by EBUS or PET scan. Because of medical comorbidities, the patient was determined not to be a candidate for surgical resection but he can tolerate chemotherapy. SOR: ↑ strong recommendation; ↓ weak recommendation; — additional considerations do not strengthen or weaken the panel's recommendation.

[a]Disagreement, that is, 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.

A, usually appropriate; EBUS, endobronchial ultrasound; EO, expert opinion; L, limited; M, may be appropriate; N/A, not applicable; PCI, prophylactic cranial irradiation; PD-L1, programmed death-ligand 1; PET, positron emission tomography; SBRT, stereotactic body radiation therapy; SOE, strength of evidence; SOR, strength of recommendation; SQ, study quality; U, usually not appropriate.

chemotherapy after SBRT seem to have superior oncologic outcomes than those who did not for T1-T2 SCLC.[15] Although there is no prospective evidence validating the role of consolidative chemotherapy after SBRT, it can be considered on the basis of extrapolation from the role of adjuvant chemotherapy after surgical resection of SCLC. Similar principles should be considered for PCI in clinical stage T1-T2 N0M0 disease as discussed previously in surgically resected disease. The panel strongly recommended that if SBRT is to be delivered, consolidative chemotherapy is usually appropriate. Our recommendations regarding SBRT for early SCLC are also in line with the American Society of Radiation Oncology Executive Summary of evidence-based guideline for early stage NSCLC with high operative risk.[16]

### *Locally Advanced SCLC (T3-T4 or N+)*

**Combined Modality Therapy With Concurrent Chemoradiation.** The panel strongly endorsed concurrent platinum doublet chemotherapy with definitive TRT as the standard of care for the initial management of locally advanced LS-SCLC (Table 3).[17] In addition to numerous randomized prospective trials, the benefit of TRT was verified by the landmark Pignon et al.[18] meta-analysis that analyzed 13 prospective randomized trials. Despite a preponderance of evidence supporting the upfront use

**Table 3.** Variant 3

| Procedure | Rating Category | Final Tabulations 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Group Median Rating | Disagree[a] | Reference | SQ | SOE | SOR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Best supportive care | U | 7 | 2 | | | | | | | | 1 | | 18 | 3 | EC | ↑ |
| Systemic platinum/etoposide chemotherapy alone | U | 5 | 3 | 1 | 1 | | | | | | 1.5 | | 18, 19 | 3, 2 | S | ↑ |
| Concurrent thoracic radiation with platinum/etoposide | A | | | | | | | | 2 | 7 | 9 | | 17, 18 | M, 3 | S | ↑ |
| Thoracic radiation alone | U | 3 | 3 | 1 | 2 | | | | | | 2 | | 18 | 3 | L | ↑ |
| Initiate thoracic radiation by cycles 1–2 of chemotherapy | A | | | | | | | 1 | 4 | 4 | 8 | | 22, 23, 24, 25, 26, 27 | M, 1, 1, 1, 1, 1 | S | ↑ |
| Consolidative anti-PD-L1-directed immune therapy after chest-directed therapy | U | 2 | | 6 | | | | 2 | | | 3 | | N/A | N/A | L | ↓ |

*Note:* A 50-year-old woman is found to have LS unresectable 6 cm right middle lobe SCLC with mediastinal station seven involvement without evidence of distant metastatic disease (AJCC stage IIIA, cT3N2M0). SOR: ↑ strong recommendation.

[a]Disagreement, that is, 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.

A, usually appropriate; AJCC, American Joint Committee on Cancer; EC, expert consensus; L, limited; LS, limited-stage; M, may be appropriate; N/A, not applicable; PD-L1, programmed death-ligand 1; SOE, strength of evidence; SOR, strength of recommendation; SQ, study quality; U, usually not appropriate.

of TRT, analyses of the National Cancer Database suggest that TRT is not utilized in half of LS-SCLC cases in the United States.[19] For these reasons, the panel recommends on the basis of both expert opinion and strong evidence that best supportive care or systemic therapy alone is not appropriate. This panel recommendation is based on studies demonstrating that without incorporation of TRT, nearly all patients progress on chemotherapy and have dismal survival.[20] The panel also reaffirmed that the early delivery of TRT is supported by multiple prospective randomized trials and meta-analysis.[21-28] Therefore, the panel strongly recommends that it is appropriate for TRT to be incorporated with curative intent no later than the second cycle of chemotherapy. Despite limited evidence, the panel strongly recommended that TRT alone (without chemotherapy) is not appropriate (unless chemotherapy is medically contraindicated), as this would likely represent a palliative treatment in a curative setting, and the panel strongly endorses curative intent when at all feasible for LS-SCLC.

Although aggressive surgical resection has historically been utilized for LS-SCLC, surgery has fallen out of favor owing to multiple clinical trials failing to reveal benefit. Before the introduction of chemotherapy, an early trial by the Medical Research Council of Great Britain randomized patients to definitive surgery versus radiation for LS-SCLC. The Medical Research Council trial revealed that radiation had significantly better survival with a median survival of 300 days compared with 199 days for surgery ($p = 0.04$).[29] A more modern intergroup trial lead by the Lung Cancer Study Group evaluated the role of trimodality therapy for LS-SCLC,[30] in which patients received induction cyclophosphamide, doxorubicin, and vincristine chemotherapy and were randomized to surgery, TRT, and PCI (trimodality) versus TRT and PCI (bimodality). There were no significant differences in survival between the arms, curbing enthusiasm for trimodality therapy. For these reasons, the panel discourages aggressive surgical management for locally advanced SCLC outside the context of a clinical trial.

**Radiation Dose and Fractionation.** One of the most controversial aspects of combined modality therapy for LS-SCLC is the optimal radiation and fractionation for TRT (Table 4). In the trial by Turrisi et al.,[31] concurrent cisplatin and etoposide with 45 Gy delivered at 1.8 Gy daily versus 1.5 Gy twice daily revealed that the twice daily treatment accelerated hyperfractionation and had superior tumor control and survival.[31] The panel recognized that a major criticism of this trial is that 45 Gy delivered once daily is not radiobiologically equivalent to 45 Gy delivered twice daily. With daily fractionation, a number of studies have used a dose of 60 Gy or more in conjunction with concurrent chemotherapy, revealing reasonable oncologic outcomes.[32,33] To determine the optimal dose, a phase 1 clinical trial determined that 70 Gy at 2 Gy once daily and 45 Gy delivered 1.5 Gy twice daily are

**Table 4.** Variant 4

| Procedure | Rating Category | Final Tabulations 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Group Median Rating | Disagree[a] | Reference | SQ | SOE | SOR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Radiation dose of 45 Gy at 1.5 Gy twice daily | A | | | | | | | 1 | 3 | 5 | 9 | | 28, 29, 31 | 1, 3, 2 | S | ↑ |
| Radiation dose of 60–70 Gy at 1.8–2.0 Gy daily | A | | | | | | | 5 | 2 | 2 | 7 | | 29, 32, 33, 37 | 3, 2, 2, 1 | S | ↑ |
| Radiation concomitant boost technique to dose of 61.2 Gy | M | | | | 4 | 1 | 3 | 2 | | | 5.5 | | 34 | 2 | L | — |
| Elective mediastinal nodal irradiation | M | | | 2 | 7 | 1 | | | | | 4 | | 35, 36 | 1, 2 | EC | — |
| Motion management (4D CT scan, breath hold, or abdominal compression) | A | | | 1 | | | | 5 | | 3 | 7 | | N/A | N/A | EC | ↑ |
| IMRT | A | | | | | | | 4 | 1 | 4 | 8 | | 38 | 2 | EC | ↑ |
| 3D-Conformal radiation therapy | M | | | | 2 | 1 | 10 | | | | 6 | | 38 | 2 | EC | — |
| Proton therapy | M | 1 | 1 | 1 | 3 | 5 | 1 | | | | 4.5 | | 39 | 3 | L | ↓ |
| Daily image guidance (kV or CBCT) | A | | | | | | | 6 | | 3 | 7 | | N/A | N/A | EC | ↑ |

*Note:* A 50-year-old man with LS-SCLC cT4N3M0 is planned to receive concurrent cisplatin/etoposide with thoracic radiation therapy. SOR: ↑ strong recommendation; ↓ weak recommendation; — additional considerations do not strengthen or weaken the panel's recommendation.

[a]Disagreement, that is, 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.

3D, three dimensional; 4D, four dimensional; A, usually appropriate; CBCT, cone beam CT scan; CT, computed tomography; EC, expert consensus; IMRT, intensity modulated radiation therapy; L, limited; LS, limited-stage; M, may be appropriate; N/A, not applicable; SOE, strength of evidence; SOR, strength of recommendation; SQ, study quality.

the maximum tolerated doses with concurrent chemotherapy.[34] Phase 2 data have also revealed favorable oncologic outcomes with a dose of 70 Gy delivered daily.[35,36] Another strategy to increase radiation dose to tumor has been to use TRT with a concomitant boost to a dose of 61.2 Gy.[37]

Two major randomized phase 3 clinical trials, the landmark European CONVERT trial and the U.S. Trial CALGB 30610/Radiation Therapy Oncology Group (RTOG) 0538 have attempted to compare fractionation schemes for LS-SCLC combined modality therapy. In the completed phase 3 CONVERT trial, 66 Gy delivered once daily (median survival of 25 mo) did not have superior outcomes compared with 45 Gy delivered twice daily (median survival of 30 mo).[38] As CONVERT was not powered to detect noninferiority, the panel did not feel that it can be concluded that 66 Gy delivered daily was equivalent to 45 Gy twice daily. In the ongoing CALGB 30610/RTOG 0538 phase III trial, subjects are being randomized to either 45 Gy twice daily or 70 Gy daily (61.2 Gy concomitant boost arm terminated owing to toxicity analysis). At the 2020 annual meeting of the American Society of Clinical Oncology, results were presented in abstract form of a Norwegian randomized phase 2 trial comparing 60 Gy versus 45 Gy twice daily, suggesting better survival in the 60 Gy arm (B. H. Gronberg et al., unpublished data), but the panel decided to not evaluate this study until final publication.

Taken together, the panel concluded that when feasible, the optimal dose and fractionation for LS-SCLC is 45 Gy delivered 1.5 Gy twice daily with concurrent chemotherapy on the basis of strong evidence. In patients for whom twice-daily fractionation is not logistically possible, there was strong panel consensus that a daily radiation to a dose of 60 to 70 Gy delivered 1.8 to 2 Gy daily fractions is usually appropriate if meeting acceptable normal tissue constraints such as a maximum esophageal dose of 66 Gy, volume of normal lung exposed to 20 Gy less than 35%, and heart volume of normal lung exposed to 40 Gy less than 30%. As for concomitant boost technique to a dose of 61.2 Gy for which there is limited evidence, the panel determined that it may be appropriate, but final results of CALGB 30610/RTOG 0538 are expected to clarify the role of this fractionation scheme if any.

**Thoracic Radiation Technique.** The panel also evaluated a number of TRT techniques in variant 4 (Table 4). Most combined modality studies that validated the role of radiation for LS-SCLC used two-dimensional techniques that irradiated large volumes of nontarget normal tissue. However, there is accumulating evidence supporting the use of technological advancements to improve tumor target coverage and sparing of nontarget organs at risk. Although comparative studies of radiation techniques in LS-SCLC are sparse with little direct evidence, the panel believes that studies on radiation techniques in locally advanced NSCLC are directly applicable to SCLC because of the same anatomical challenges and normal tissue considerations. Thus, despite a paucity of evidence, the panel did generate a number of strong recommendations on the basis of expert consensus.

For target delineation, the panel recommends patients to undergo PET/CT scan and mediastinal evaluation with endobronchial ultrasound or mediastinoscopy to generate an accurate gross tumor volume. At the time of radiation in CT simulation, the panel strongly recommended on the basis of expert consensus that motion management with either a four-dimensional CT scan, respiratory gating, breath hold, or abdominal compression is usually appropriate. In developing a clinical target volume (CTV), reasonable margins are to include 5 to 8 mm beyond the gross tumor volume to account for occult microscopic disease while respecting anatomical boundaries. There are several lines of evidence revealing that elective nodal irradiation (ENI) is unnecessary. When using PET scans for involved nodal irradiation in SCLC, a prospective study revealed only a 3% marginal failure rate.[39] Furthermore, in the completed CONVERT trial that achieved oncologic results as good as or better than historic controls, ENI was not permitted.[40] In the ongoing CALGB 30610/NRG Oncology RTOG 0538 trial, the CTV similarly does not include elective mediastinal nodal stations. On the basis of these rationales, the panel recommends against including ENI when developing the CTV in properly staged patients. From the CTV, a planning target volume based on institutional set-up uncertainty should be generated (typically in the range of 5–7 mm with daily image guidance) with radiation dose prescribed to adequately cover the planning target volume. The panel also strongly recommended that daily image guidance with kV films or cone beam CT scan be used on the basis of expert consensus.

Although three-dimensional CRT and intensity modulated radiation therapy (IMRT) have not been prospectively compared in LS-SCLC, IMRT has been reported to have a lower likelihood of severe pneumonitis in the definitive treatment of locally advanced NSCLC.[41] As the anatomy and normal tissue constraints are identical for locally advanced NSCLC and LS-SCLC, the panel strongly recommends that use of IMRT is usually appropriate on the basis of expert opinion to reduce the likelihood of severe radiation-related toxicity, recognizing that there is little evidence on technique in SCLC itself. The panel also determined with a weaker recommendation that three-dimensional CRT may be appropriate depending on clinical urgency and tumor size.

Radiation plan optimization should prioritize maximizing conformity of high-dose regions such as the volume of normal lung exposed to 20 Gy.[41] Finally, there has been interest in using particle therapy for thoracic malignancies with one encouraging prospective study reported,[42] and further exploration of proton or heavy ion therapy for is encouraged by the committee.

**PCI After Chemoradiation for LS-SCLC.** PCI after thoracic chemoradiation has generally been accepted as a standard of care for LS-SCLC (Table 5). The meta-analysis of Auperin et al.[8] of 17 trials that included 987 patients revealed that PCI not only reduced brain metastases but was also associated with an absolute overall survival benefit of 5.4%. Although the premise of the meta-analysis of Auperin et al.[8] was that roughly 50% of patients develop brain metastases, the major criticism of this assumption is that the included studies predated the use of MRIs for metastatic work-up. However, as PCI is a potentially curative modality, the panel strongly recommends that PCI is usually appropriate on the basis of strong evidence. As for MRI surveillance every 3 months, the panel also felt this to be an appropriate strategy in lieu of PCI despite limited evidence. However, the panel felt that observation without PCI or MRI surveillance is usually not appropriate owing to the high propensity for brain metastases in SCLC.

The optimal dose for PCI has also been a subject of debate.[8] In the trial of Turrisi et al.,[31] the PCI dose was 25 Gy delivered in 10 fractions. An international intergroup study evaluated the potential role of dose escalation of PCI.[43] In the PCI trial of Le Péchoux et al.,[43] patients were randomized to 25 Gy in 10 fractions or 36 Gy delivered either in 2 Gy daily or 1.5 Gy twice daily fractions, and 36 Gy unexpectedly neither reduced brain metastases nor improved survival compared with 25 Gy. Similarly, the meta-analysis of Auperin et al.[8] revealed that higher PCI doses were not associated with a survival benefit. Thus, the panel determined that PCI to a dose of 25 Gy delivered in 10 fractions is usually appropriate and that other dose escalated fractionation schemes are usually not appropriate.

Although PCI has been revealed to reduce brain metastases and improve survival, it is also associated with neurocognitive toxicity, and there is ongoing interest in exploring strategies to reduce such side effects while still employing radiotherapy to reduce central nervous system failure. An analysis of RTOG 0212 revealed that more than 60% of patients experienced neurocognitive deterioration after.[44] As the hippocampus is a source of neural stem cells that are critical for memory and neuroplasticity, the role of hippocampal avoidance using IMRT for brain metastases and PCI is currently the subject of the ongoing NRG Oncology Trial CC003. However, as whole-brain PCI is a potentially curative modality, the panel recommends that PCI with hippocampal avoidance be offered in the context of a clinical trial for at this time. The panel felt that IMRT with hippocampal avoidance might be appropriate pending further study. As blockade of the N-methyl-D-aspartic acid neurotransmitter receptor with memantine reduces neurocognitive side effects after whole-brain irradiation,[45] the panel rated the use of memantine in conjunction with PCI to be usually appropriate despite limited evidence with PCI. In addition, for patients with history of neurocognitive deficit/disorder, stroke, or seizure disorder, it is reasonable to defer PCI, in favor of a surveillance strategy, as such patients were specifically excluded from modern PCI trials.[43]

**Table 5.** Variant 5

| Procedure | Rating Category | Final Tabulations 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Group Median Rating | Disagree[a] | Reference | SQ | SOE | SOR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Observation without CNS imaging surveillance | U | 2 | 1 | 6 | 1 | | | | | | 3 | | N/A | N/A | EO | — |
| Surveillance MRI of brain every 3 mo | A | | | | | 1 | 2 | 8 | 1 | 1 | 7 | | N/A | N/A | EO | ↓ |
| PCI 25 Gy in 10 fractions | A | | | 1 | | | | 4 | 5 | | 7.5 | | 8, 28, 40 | M, 1, 1 | S | ↑ |
| PCI 36 Gy at 1.5-2 Gy per fraction | U | 2 | 1 | 5 | 1 | 1 | | | | | 3 | | 40, 41 | 1, 1 | S | ↑ |
| PCI with intensity modulated radiation for hippocampal avoidance | M | 1 | | | 1 | 3 | 3 | 1 | | | 5 | | N/A | N/A | L | ↓ |
| Administration of memantine with PCI | M | | | | 2 | | 6 | 2 | | | 6 | | 42 | 1 | L | — |

*Note:* A 70-year-old man completes concurrent cisplatin/etoposide and thoracic radiation for LS-SCLC. A PET scan 3 months after radiation reveals complete metabolic response of thoracic disease without distant metastases and an MRI of the brain with contrast reveals no brain metastases. SOR: ↑ strong recommendation; ↓ weak recommendation; — additional considerations do not strengthen or weaken the panel's recommendation.

[a]Disagreement, that is, 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.

A, usually appropriate; CNS, central nervous system; EO, expert opinion; L, limited; LS, limited-stage; M, may be appropriate; MRI, magnetic resonance imaging; N/A, not applicable; PCI, prophylactic cranial irradiation; PET, positron emission tomography; S, strong; SOE, strength of evidence; SOR, strength of recommendation; SQ, study quality; U, usually not appropriate.

### Immune Therapy for LS-SCLC

In addition to concurrent chemoradiation, there is substantial interest in incorporating programmed cell death protein-1 and programmed death-ligand 1 (PD-L1)–directed immune therapy in the management of LS-SCLC (Tables 1–3 and 5). Although the anti–PD-L1 antibody atezolizumab has activity and improves survival in extensive-stage SCLC,[46] evidence justifying use of checkpoint inhibition remains immature. Currently, the phase 2 randomized STIMULI (small cell lung carcinoma trial with nivolumab and ipilimumab in limited disease) trial and another phase 1 trial (NCT02402920) are evaluating the role of checkpoint inhibitors for LS-SCLC,[47] and a larger randomized prospective trial is underway (NRG Oncology LU-005). At this time, the panel does not recommend the use of immune therapy outside the context of a prospective clinical trial for LS-SCLC.

## Discussion

The ARS Thoracic AUC have developed consensus guidelines on appropriate multidisciplinary management of LS-SCLC. Although the these guidelines are largely in line with the American Society of Radiation Oncology and the National Comprehensive Cancer Network,[17,48,49] these ARS AUC guidelines provide novel ratings on the appropriateness of radiation in the context of surgical management, PCI with hippocampal avoidance, ENI, radiation image guidance, respiratory motion management, radiation dose constraints, IMRT, proton therapy, and PD-L1–directed immune therapy. As such, these 2020 ARS AUC guidelines for LS-SCLC aim to serve as a groundwork for multidisciplinary management and future clinical trials.

### Summary of Recommendations

The ARS provides the following conclusions and summary recommendations for LS-SCLC:

- The panel recommends strongly that adjuvant mediastinal radiation is usually not appropriate for the typical case with surgically resected pT1-T2N0M0 SCLC with negative margins (variant 1).
- The panel recommends strongly that concurrent chemotherapy and thoracic radiation are usually appropriate, and the panel recommends with reservations that SBRT followed by consolidative chemotherapy may be appropriate for the typical case with medically unresectable early stage SCLC (variant 2).
- The panel recommends strongly that concurrent chemotherapy and thoracic radiation followed by PCI are usually appropriate for the typical case with unresectable node-positive LS-SCLC (variant 3).
- The panel recommends strongly that radiation therapy to a dose of 45 Gy at 1.5 Gy twice daily or 60 to 70 Gy at 1.8 to 2 Gy daily delivered by means of IMRT with motion management and daily image guidance is usually appropriate for the typical case with unresectable node-positive LS-SCLC (variant 4).
- The panel recommends strongly that PCI to a dose of 25 Gy delivered in 10 fractions is usually appropriate, and the panel recommends with reservations that brain MRI surveillance may be appropriate for the typical case with LS-SCLC (variant 5).

### Summary of Evidence

Of the 47 references cited, there were 14 well-designed studies (randomized prospective clinical trials), nine moderately well-designed studies, 11 studies with design limitations, four meta-analyses, eight studies that were not classified as primary references, and one protocol description. These references were published between 1970 and 2019 (Supplementary Appendix).

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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.2020.10.020.

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