doi.org/10.58931/cot.2025.2239

About the Author

Nathalie Daaboul, MD, FRCPC

Dr. Nathalie Daaboul received her medical degree, followed by her hematology and medical oncology training at Université de Montreal. She continued with a clinical research fellowship in thoracic oncology at the Ottawa Hospital Cancer Center. She is currently practicing at the Centre Intégré de Cancérologie de la Montérégie, at Hôpital Charles LeMoyne, with an interest in lung and upper GI cancers. She is also an associate professor at the Université de Sherbrooke.

Affiliations: Centre intégré de Cancérologie de la Montérégie, Hôpital Charles LeMoyne, Université de Sherbrooke, Québec

Small-Cell Lung Cancer: Integration of Radiation and Immunotherapy for All Stages

Nathalie Daaboul, MD, FRCPC

Small cell lung cancer is an aggressive cancer with a poor prognosis. New treatment paradigms have developed with the incorporation of new therapies in the last few years, aiming to improve patient survival. Some emerging therapies include the addition of immunotherapy to chemotherapy. This article provides a practical review of the current and upcoming treatment options for SCLC in both limited and extensive stages, focusing on integrating radiation and immunotherapy.

Introduction

Epidemiology and Staging of SCLC

Small cell lung cancer (SCLC) is a highly aggressive subtype of neuroendocrine tumours, accounting for approximately 15% of all lung cancer cases.[1] In Canada, an estimated 32,100 Canadians were expected to be diagnosed with lung cancer in 2024.[2] The incidence of SCLC is slowly declining, largely due to reduced tobacco use, as over 95% of patients diagnosed with SCLC have a history of tobacco use.[1,2]

Staging of SCLC is commonly based on the Veterans Administration Lung Group (VALG) classification, which categorizes the disease into two stages. Limited stage is defined as cancer that is confined to one hemithorax and regional lymph nodes, including ipsilateral mediastinal and supraclavicular nodes, and can be encompassed within a single radiation field. Extensive stage, on the other hand, is defined as disease that has spread beyond these regions, including distant metastases or malignant pleural/pericardial effusions. Further, the TNM classification can also be used to stage SCLC.

SCLC is often diagnosed at an advanced stage. Approximately 70% of patients present with extensive-stage disease, for which a curative treatment is no longer possible. Unfortunately, symptoms are usually hard to detect, and the cancer progresses rapidly. Some presenting elements include respiratory symptoms, such as dyspnea, cough, hemoptysis, or systemic symptoms, such as fatigue and weight loss.

Treatment Guidelines for Limited Stage SCLC (LS-SCLC)

Surgical Considerations

Surgery remains controversial in LS-SCLC, but may be considered for very limited stage disease, particularly small tumours without nodal involvement. Often, the diagnosis is made postoperatively when no preoperative biopsy was performed. In such cases, adjuvant chemotherapy, with or without radiotherapy, is required. However, many clinicians would consider chemoradiotherapy (CRT) over surgery. When considering surgery as the main treatment modality, it is advised to present a patient's case in a multidisciplinary tumour board.

Standard of Care: Chemotherapy and Radiotherapy

Chemotherapy

The standard treatment for LS-SCLC involves a combination of chemotherapy and thoracic radiotherapy. The typical regimen includes four cycles of a platinum doublet (cisplatin and etoposide). Cisplatin's main adverse events include myelosuppression, nausea/vomiting, and renal toxicity. Carboplatin can substitute cisplatin in patients with significant comorbidities or advanced age disease.[3,4]

Concurrent administration of chemotherapy and radiotherapy (CRT) is preferred, as it has been shown to be superior to chemotherapy alone in the treatment of LS-SCLC. Chemotherapy monotherapy is not curative and primarily serves a radio-sensitizing role, enhancing the effectiveness of radiotherapy, and it has the potential to decrease micrometastases.

Radiotherapy

Evidence suggests that the earlier radiotherapy is initiated during the treatment course, the better the disease control. Radiotherapy is often started with the second cycle of chemotherapy. Moreover, CRT has also demonstrated superior outcomes compared to a sequential delivery, where radiotherapy follows the completion of chemotherapy.[5,6]

There is significant variability in the administration of thoracic radiotherapy for LS-SCLC across Canada and internationally. Some studies suggest that twice-daily radiotherapy may offer a survival advantage over once-daily regimens.[5] However, no significant differences in overall survival have consistently been demonstrated between these two concurrent modalities in clinical trials. The choice of a radiotherapy schedule often depends on institutional logistics, the capacity of cancer centres, and the ease of access for patients.[3,4] In many jurisdictions, especially in Canada, once-daily radiotherapy remains the preferred approach due to practical considerations and patient convenience.

Prophylactic brain irradiation (PCI) may be considered in patients who have achieved a good response to initial CRT. The rationale for PCI is that it may reduce the incidence of brain metastases. Recommendations for PCI are mainly based on a meta-analysis from the pre-magnetic resonance imaging (MRI) era, which demonstrated a 5.4% improvement in overall survival at 3 years for patients receiving PCI compared to controls.[7] However, a large retrospective study challenged these findings, showing no statistically significant survival benefit for patients receiving PCI vs. those in the observation arm (hazard ratio [HR]: 0.90; $p = 0.29$).[8] Therefore, the practice of using PCI is declining in favour of serial MRI imaging.

ADRIATIC Trial and Durvalumab Consolidation

Despite CRT, LS-SCLC remains associated with a poor prognosis, with a median survival of approximately two years and high recurrence rates. Long-term survival is rare, and most patients eventually develop distant metastases, often involving the central nervous system.

The ADRIATIC trial is a Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy of durvalumab, with or without tremelimumab, as consolidation therapy in patients with LS-SCLC who did not progress following concurrent CRT.[9] Patients included had received chemotherapy treatment consisting of cisplatin/carboplatin with etoposide, and radiation protocols included a standard once-daily schedule of 60–66 Gy over 6 weeks or hyperfractionated radiotherapy twice-daily at 45 Gy over 3 weeks. Patients were allowed to start the trial treatment 1–42 days after the completion of radiotherapy. Maintenance durvalumab (or placebo) was administered every 4 weeks until disease progression, unacceptable toxicity, or up to 24 months.

At an interim analysis in 2024, consolidation therapy with durvalumab was found to significantly improve overall survival compared to placebo. The median overall survival (mOS) was 55.9 months (durvalumab) vs. 33.4 months (placebo); (HR: 0.73; 95% confidence interval [CI]: 0.57–0.93). The median progression-free survival (mPFS) was 16.6 months (durvalumab) vs. 9.2 months (placebo); (HR: 0.76; 95% CI: 0.61–0.95). The treatment assessed in the ADRIATIC trial is the first treatment shown to improve survival since the introduction of CRT and has now emerged as a new standard of care for patients with LS-SCLC who did not progress after concurrent CRT. No new safety concerns were reported, and durvalumab has been approved in many jurisdictions for this indication.

Treatment Guidelines for Extensive-Stage SCLC (ES-SCLC)

The standard first-line treatment for ES-SCLC involves a combination of chemotherapy and immunotherapy. Doublet platinum with etoposide is the chemotherapy regimen of choice, but yields limited survival benefits, with prognosis rarely surpassing a year. The introduction of immunotherapy in the form of immune checkpoint inhibitors (ICI) has changed the treatment landscape, and the combination of chemotherapy and immunotherapy is now considered the standard of care.[3,4]

Immunotherapy

Two trials (Phase III, randomized, double-blind, placebo-controlled studies: IMpower 133 and CASPIAN) justify the addition of immunotherapy to treatment regimens for ES-SCLC.[10,11] In both trials, patients received immunotherapy (anti-programmed cell death ligand 1 [PD-L1] ICI) in combination with doublet platinum chemotherapy for 4 cycles, if they had a good performance status and no contraindications to the use of immunotherapy. In patients without documented disease progression after this regimen, ICI treatment could be continued as maintenance therapy.

IMpower133 compared atezolizumab + carboplatin + etoposide vs. placebo + chemotherapy (both: 4 cycles).[10] The addition of ICI improved mOS to 12.3 months (atezolizumab) vs. 10.3 months for placebo (HR: 0.70; 95% CI: 0.54–0.91). The CASPIAN trial compared durvalumab + cisplatin/carboplatin + etoposide (4 cycles) vs. placebo + chemotherapy (4–6 cycles).[11] The addition of ICI in this study also improved mOS to 12.9 months compared to 10 months in the placebo group (HR: 0.71; 95% CI: 0.62–0.91). The study also included a third arm with durvalumab + tremelimumab + chemotherapy that did not add any benefit.

Long-term survivors were observed in both studies, with some patients maintaining durable responses beyond 3 years. No significant increase in toxicity was reported with the addition of immunotherapy compared to chemotherapy alone.[10,11] Both trials reinforce immunotherapy with a platinum doublet as a standard of care in ES-SLCLC.[3,4]

Maintenance with Lurbinectedin

Even with the addition of immunotherapy, patient outcomes remain poor and other strategies are being studied to improve survival. One of the strategies is adding a new agent to the maintenance phase. Before immunotherapy became standard in first-line treatment, it was assessed in the maintenance phase, with no success. Recently, primary data from the IMforte trial were presented. This study is a Phase III, randomized clinical study that evaluates the efficacy of lurbinectedin, a synthetic alkaloid chemotherapy, in combination with atezolizumab as maintenance therapy in patients with ES-SCLC who have not progressed after first-line induction therapy.

The combination of lurbinectedin and atezolizumab demonstrated statistically significant improvements in both mPFS at 5.4 months vs. 2.1 months (HR: 0.54; 95% CI: 0.43–0.67) and mOS (13.2 months vs. 10.6 months; HR: 0.73; 95% CI: 0.57–0.95) compared to atezolizumab alone. The addition of lurbinectedin is therefore a new treatment option, but comes with more adverse events, mostly cytopenias and febrile neutropenia. Other immunotherapy maintenance strategies are under study, such as strategies that include the addition of T-cell engagers and vaccines.

Radiotherapy

As discussed previously, the main treatment modality for ES-SCLC is chemotherapy with immunotherapy, but radiotherapy can be considered in specific circumstances.

Thoracic radiotherapy (TRT) was studied in the CREST trial in patients with ES-SCLC who had responded to initial chemotherapy.[13] The trial did not meet its primary endpoint of improving 1-year

overall survival, but had a signal of improved 2-year survival. However, it reduced the risk of intrathoracic recurrence, particularly in patients with low residual tumour burden, very good response to chemotherapy, and persistent thoracic disease. TRT was excluded from the IMpower133 and CASPIAN trials. Data justifying its routine use and robust safety data are lacking. Therefore, it can be considered on a case-by-case basis, after careful discussion, ideally in a multidisciplinary tumour board.[3,4]

PCI was studied in the EORTC 2007 trial, in which patients were randomized between PCI and observation.[14] In this study, PCI reduced the incidence of symptomatic brain metastases with a mOS of 6.7 vs. 5.4 months for the observation group. A limitation of this trial was the absence of a mandatory brain MRI prior to PCI. A Japanese Phase III trial in 2017 similarly compared PCI with observation, but included brain MRI.[15] This study found no OS benefit, which led to the conclusion that routine PCI is not necessary if MRI surveillance is available. The treatment guidelines note that PCI may be considered in patients with ES-SCLC who have had a good response to chemotherapy and no brain metastases. However, in practice, most clinicians seem to favour surveillance with brain MRI as PCI may not improve survival but might result in toxicities, including neurotoxicity and cognitive effects.[3,4]

Emerging Therapies

The most commonly used second-line treatment for ES-SCLC is topotecan, with a small benefit observed compared to supportive care[16] and similar efficacy to the CAV regimen (cyclophosphamide, doxorubicin, and vincristine).[17] The mOS achieved by this treatment was estimated to be 25 weeks. However, in 2025, the DeLLphi-304 trial, a Phase III, randomized, open-label study, showed improved survival with tarlatamab compared to topotecan.[18] Tarlatamab is a T-cell engager (TCE) targeting delta-like ligand 3 (DLL3). It has shown interesting activity in third-line or further lines of treatment in the DeLLphi-301 study, resulting in a mPFS of 4.9 months and mOS of 14.3 months.[19] In the second line in the DeLLphi-304 trial, tarlatamab was compared to standard chemotherapy in patients who progressed after one prior platinum-based chemotherapy (with immunotherapy if applicable). The mOS improved to 13.6 months with tarlatamab vs. 8.3 months with chemotherapy (HR: 0.60; 95% CI: 0.47 to 0.77). These data have resulted in it becoming a new standard of care in the second-line setting. Tarlatamab's toxicity profile is different from chemotherapy, as cytokine release syndrome (CRS) or immune effector cell-associated neurotoxicity syndrome (ICANS) have been reported, though most were grades 1–2.[18]

Conclusion

The treatment of SCLC has changed in the last few years. In LS-SCLC, the backbone remains chemoradiotherapy, administered concurrently if possible. The addition of durvalumab as a consolidation treatment has significantly increased survival and has become the new standard of care. In ES-SCLC, the combination of immunotherapy (atezolizumab or durvalumab) with a platinum doublet chemotherapy is routinely used. Radiotherapy with TRT or PCI can be considered on a case-by-case basis. New emerging strategies have also been shown to improve survival, and include the addition of lurbinectedin in the maintenance phase or the modification of second-line treatment or beyond with TCEs, such as tarlatamab. Supportive and multidisciplinary care remain crucial in SCLC to improve outcomes and help maintain patients' quality of life.

Correspondence

Nathalie Daaboul, MD, FRCPC
Email: nathalie.daaboul@usherbrooke.ca

Financial Disclosures

N.D.: None declared.

References

1. Lung Cancer Canada. 2024 Faces of lung cancer report [Internet]. Toronto (ON): Lung Cancer Canada; 2024 [cited Jun 22 2025].
2. Statistics Canada. Lung cancer is the leading cause of cancer death in Canada [Internet]. Ottawa (ON): Statistics Canada; 2022 Jan 4 [cited Jun 22 2025].
3. Früh M, Garassino MC, Dziadziuszko R, Peters S. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2024;35(Suppl 2):ii102–ii115.
4. Kalemkerian GP, Loo BW Jr, Akerley W, Attia A, Boumber Y, Decker RH, et al. Therapy for stage IV small-cell lung cancer: ASCO living clinical practice guideline. J Clin Oncol. 2023;41(30):3315–30.

5. Turrisi AT 3rd, Kim K, Blum R, Sause WT, Livingston RB, Komaki R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med. 1999;340(4):265–71.
6. Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: JCOG 9104. J Clin Oncol. 2002;20(14):3054–60.
7. Auperin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. N Engl J Med. 1999;341(7):476–84.
8. Chen, Y., Wang, Y., Ren, F. et al. Prophylactic cranial irradiation (PCI) versus active surveillance in patients with limited-stage small cell lung cancer: a retrospective, multicentre study. Respir Res 23, 274 (2022). https://doi.org/10.1186/s12931-022-02196-2.
9. Cheng Y, Spigel DR, Cho BC, Laktionov KK, Fang J, Chen Y, Zenke Y, et al. Durvalumab after chemoradiotherapy in limited-stage small-cell lung cancer. N Engl J Med. 2024;391(13):1313–1327. doi:10.1056/NEJMoa2404873.
10. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–9. doi:10.1056/NEJMoa1809064.
11. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, 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(10212):1929–39. doi:10.1016/S0140-6736(19)32222-6.
12. Paz-Ares L, Borghaei H, Liu SV, Peters S, Herbst RS, Stencel K, et al. Lurbinectedin plus atezolizumab as first-line maintenance therapy in extensive-stage small-cell lung cancer: primary results from the phase 3 IMforte trial. J Clin Oncol. 2025;43(Suppl 15):LBA8500. Presented at: ASCO Annual Meeting; 2025 Jun 2–6; Chicago, IL.
13. Slotman BJ, van Tinteren H, Praag JO, Knegjens JL, El Sharouni SY, Hatton M, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet. 2015;385(9962):36–42. doi:10.1016/S0140-6736(14)61085-0.
14. Slotman BJ, Faivre-Finn C, Kramer GWPM, Rankin EM, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. 2007;357(7):664–72. doi:10.1056/NEJMoa071780.
15. 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(5):663–71. doi:10.1016/S1470-2045(17)30110-1.
16. O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cucevià B, Juhasz G, et al. Phase III trial comparing supportive care alone with supportive care with oral or intravenous topotecan in patients with relapsed small-cell lung cancer. Lancet. 2004;364(9441):192–9. doi:10.1016/S0140-6736(04)16684-0.
17. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol. 1999;17(2):658–67.
18. Rudin CM, Mountzios G, Sun L, Cho BC, Demirci U, Baka S, et al. Tarlatamab versus chemotherapy as second-line treatment for small cell lung cancer: primary analysis of the phase 3 DeLLphi-304 trial. J Clin Oncol. 2025;43(Suppl 17):LBA8008. doi:10.1200/JCO.2025.43.17_suppl.LBA8008.
19. Ahn MJ, Cho BC, Felip E, Korantzis I, Ohashi K, Majem M, et al. Tarlatamab for patients with previously treated small-cell lung cancer. N Engl J Med. 2023;389(22):2063–75. doi:10.1056/NEJMoa2307980.

Canadian Oncology Today
Science for the Real World

canadianoncologytoday.com

1.