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Review

Limited-Stage Small-Cell Lung Cancer: Current Progress and the Next Frontier

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Simple Summary: Limited-stage (LS) small-cell lung cancer (SCLC) is a type of lung cancer that is confined to one side of the chest without cancer spread elsewhere. The outcomes of patients with this disease remain poor. Currently, patients with LS-SCLC are managed with chemotherapy and radiotherapy that is delivered together. In this review article, we highlight various advancements in treatments for LS-SCLC patients and challenges that are required to be overcome to achieve better patient outcomes.

Abstract: Limited-stage (LS) small-cell lung cancer (SCLC) is defined as disease confined to a tolerable radiation portal without extrathoracic metastases. Despite clinical research over two decades, the prognosis of LS-SCLC patients remains poor. The current standard of care for LS-SCLC patients is concurrent platinum-based chemotherapy with thoracic radiotherapy (RT). Widespread heterogeneity on the optimal radiation dose and fractionation regimen among physicians highlights the logistical challenges of administering BID regimens. Prophylactic cranial irradiation (PCI) is recommended to patients following a good initial response to chemoradiation due to improved overall survival from historical trials and the propensity for LS-SCLC to recur with brain metastases. However, PCI utilization is being debated due to the greater availability of magnetic resonance imaging (MRI) and data in extensive-stage SCLC regarding close MRI surveillance in lieu of PCI while spurring novel RT techniques, such as hippocampal-avoidance PCI. Additionally, novel treatment combinations incorporating targeted small molecule therapies and immunotherapies with or following radiation for LS-SCLC have seen recent interest and some concepts are being investigated in clinical trials. Here, we review the landscape of progress, limitations, and challenges for LS-SCLC including current standard of care, novel radiation techniques, and the integration of novel therapeutic strategies for LS-SCLC.

Keywords: limited-stage; small-cell lung cancer; radiotherapy; small molecules; immunotherapy; clinical trials

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1. Introduction

Small-cell lung cancer (SCLC) is a subtype of lung cancer accounting for 13–15% of all lung cancer patients [1,2]. SCLC is much more prevalent in smokers [3]. Though formally staged by the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM classification, pragmatically SCLC patients are grouped using the Veterans Administration Lung Study Group two-stage system, dividing the cancer into limited-stage and extensive-stage disease. Limited-stage SCLC (LS-SCLC) is cancer on the ipsilateral hemithorax encompassable within a tolerable radiation portal and therefore is

eligible for curative intent treatment. Extensive-stage SCLC (ES-SCLC) is cancer that either spreads widely throughout the lungs, non-regional lymph nodes or to other organs [1]. Around 30% of patients with SCLC present with LS-SCLC [4].

Overall survival (OS) rates for SCLC patients remain particularly low. For LS-SCLC patients, 5-year OS is about 20–35% [5,6]. The current standard of care for the treatment of LS-SCLC is platinum-based chemotherapy with early concurrent thoracic radiation therapy followed by prophylactic cranial irradiation (PCI) for LS-SCLC patients with good response to initial treatment [4]. Here, we review the landscape of progress, limitations, and challenges for LS-SCLC including current standard of care, novel radiation techniques, and the integration of novel therapeutic strategies for LS-SCLC.

2. Current Role of Radiation in Managing LS-SCLC

2.1. Concurrent Chemotherapy with Thoracic Radiation

Concurrent thoracic chemoradiation is the mainstay of treatment for LS-SCLC receiving treatment for curative intent. The current backbone chemotherapy regimen for LS-SCLC patients is a platinum agent with etoposide [4,7].

Concurrent chemoradiotherapy was not firmly established until the early 1990s as clinical trials attempting to investigate this approach were not significantly powered. Two meta-analyses published in 1992 established concurrent chemoradiation improved OS and local disease control [8,9]. The larger of these meta-analyses, by Pignon et al. [9], included 13 clinical trials and 2140 LS-SCLC patients with a median follow up of 43 months showed chemoradiation improved OS at 3 years by 5.4% compared to chemotherapy solely [9].

Early radiotherapy versus late radiotherapy for LS-SCLC had been previously debated. A previous study showed late radiotherapy resulted in a higher risk of brain metastasis compared to early radiotherapy (28% vs. 18%) [10]. Early thoracic radiation for LS-SCLC patients also results in better 3-year progression-free survival (PFS), 3-year OS, and 5-year OS compared to late thoracic radiation (26% vs. 19%, 30% vs. 22%, and 20% vs. 11%, respectively) [10]. A meta-analysis by Fried et al. evaluated the use of early versus late delivery of thoracic radiotherapy to LS-SCLC patients. Seven randomized controlled trials were evaluated which collectively showed 5% OS benefit at 2-years for early radiotherapy [11].

2.2. Optimal LS-SCLC Radiation Fractionation

Radiotherapy dose fractionation for LS-SCLC has a long history of clinical trial development. Published in 1999, Turrisi et al. [5] randomized 417 patients to groups that either received hyperfractionated, twice-daily (BID) radiotherapy (1.5 Gy in 30 fractions) or a regular fractionated once-daily regimen (1.8 Gy in 25 fractions) to receive a total of 45 Gy. They showed that there was a significant difference with median survival; 19 months for the once-daily group and 23 months for the BID group with an increased rate of grade 3 esophagitis [5].

Published in 2017, the CONVERT trial did not show improved survival with the once-daily fractionation to 66 Gy when compared to the 45 Gy in 30 fractions BID regimen [6]. The CALGB 30610/RTOG 0538 trial is evaluating high-dose once-daily 70 Gy thoracic radiotherapy in comparison to the 45 Gy in 30 fractions BID regimen of thoracic radiotherapy in LS-SCLC patients. The abstract reported June 2021 concluded that the 70 Gy arm did not improve OS for LS-SCLC patients [12]. Though not designed as non-inferiority studies, these two trials suggest that patients treated with once-daily fractionation appear to have similar outcomes as patients treated with 45 Gy in 30 fractions BID.

Published in 2021, a randomized phase II clinical compared the efficacy of 45 Gy in 30 fractions BID to high-dose 60 Gy in 40 fractions BID in LS-SCLC patients. Two-year survival was higher in the 60 Gy group with 74.2% of patients alive compared to 48.1% in the 45 Gy group. The rates of toxicity between the two groups also did not differ significantly [13]. Further prospective studies will be required to establish the benefit of higher dose and fractionation in LS-SCLC patients.

Despite the 45 Gy in 30 fractions BID regimen being supported with randomized trial evidence, pragmatically, heterogeneity in clinical practice and utilization exists. A pan-Canadian survey of radiation oncologists was carried out in 2016 where responses from 52 radiation oncologists were further analyzed. For LS-SCLC patients, the most common dose and fractionation schedule most commonly used by Canadian radiation oncologists was 40–45 Gy in 15 once-daily fractions (40% of respondents), followed by 45 Gy in 30 BID fractions (just over 30% of respondents). 50 Gy in 25 once-daily fractions and 60–66 Gy in 30–33 once-daily fractions were also reported at similar rates among respondents (about 10% each, respectively) [14]. This heterogeneity of regimens and the prevalence of 40–45 Gy in 15 once-daily fractions is likely informed by historical precedent as evidenced by a Canadian randomized controlled trial reported in 1993 [10]. Interestingly, a retrospective study in 2021 comparing 40 Gy in 15 fractions once daily versus 45 Gy in 30 fractions BID showed no difference in OS, locoregional recurrence, or ≥grade 3 toxicities in LS-SCLC following propensity score adjustment [15].

A US-based survey of 309 radiation oncologists showed 60% of respondents stated they preferred a once-daily thoracic radiation regimen and 76% stated that a once-daily regimen was more common in clinical practice. 54.4% of respondents preferred a 60 Gy dose when administering once-daily thoracic radiotherapy followed by 20.4% having a preference of 66 Gy. 87.9% of US radiation oncologists preferred a total dose of 45 Gy when administering BID thoracic radiotherapy. Respondents from academic institutions had a higher likelihood of endorsing BID treatment in clinical practice (51% in academic institutions vs. 33% in private practice) [16]. These surveys highlight the logistical burden of BID schemas and preferences by physicians and patients for once-daily fractionation in clinical care. Studies evaluating the optimal dose and fractionation regimen for LS-SCLC patients are summarized in Table 1.

Table 1. Studies that evaluated the optimal dose and fractionation regimen for LS-SCLC patients with study information and key findings.

Study	Total Cohort of LS-SCLC Patients	Intervention vs. Control	Endpoints	Key Findings (Intervention vs. Control)	Statistics (Intervention vs. Control)
Prospective Studies for Radiotherapy Fractionation					
Turrisi et al., 1999 [5]	417	Twice-daily 45 Gy in 30 fractions vs. once-daily 45 Gy in 25 fractions thoracic radiotherapy	Median OS 2-year survival 5-year survival	23 vs. 19 months 47% vs. 41% 26% vs. 16%	
Faivre-Finn et al., 2017 [6]	547	Twice-daily 45 Gy in 30 fractions vs. once-daily 66 Gy in 33 fractions thoracic radiotherapy	Median OS 2-year survival	30 months vs. 25 months 56% vs. 51%	95% CI 24–34 months vs. 21–31 months 95% CI 50–62% vs. 45–57%
Grønberg et al., 2020 [17]	176	Twice-daily 60 Gy in 40 fractions vs. 45 Gy in 30 fractions thoracic radiotherapy	Median OS 2-year survival	42 months vs. 23 months 73% vs. 46%	95% CI, 32–51 months vs. 17–28 months 95% CI 32–51% vs. 36–60%
Bogart et al., 2021 [12]	638	45 Gy in 30 fractions BID thoracic radiotherapy [ref] vs. once-daily 70 Gy in 35 fractions	OS	HR 0.94	95% CI, 0.76–1.2

2.3. The Role of Prophylactic Cranial Irradiation

Given the tendency for subsequent development of brain metastases from SCLC, prophylactic cranial irradiation (PCI) has been recommended to LS-SCLC patients following a good response to initial treatment with chemoradiation. The role of PCI in managing LS-SCLC is significant; it has been shown to improve the rates of brain metastasis control and OS [18].

While PCI has shown clinical benefit in LS-SCLC patients to reduce the rate of brain metastasis and improve OS, randomized prospective studies for ES-SCLC and retrospective studies for LS-SCLC have also suggested that the improved sensitivity of magnetic resonance imaging (MRI) and increased use of close imaging surveillance may diminish the resulting OS benefit of PCI [19,20]. A 2017 phase III randomized trial for ES-SCLC showed PCI improved the 1-year brain metastasis rate to 33% from 59%, however, there was a lack of OS benefit with PCI as compared to the MRI surveillance only arm [20]. Further investigations remain to ascertain whether PCI provides an OS benefit with the availability of MRI and uptake of close imaging surveillance for LS-SCLC patients. According to retrospective studies, another subgroup of LS-SCLC patients where the absolute benefit of PCI may be lower are LS-SCLC patients with AJCC stage I-II disease, highlighting the importance of obtaining TNM classification and stage for all SCLC patients [21,22].

PCI utilization rates have not been consistent and are known to differ between institutions (Table 2). A retrospective study at the Princess Margaret Cancer Centre showed improvements in OS and brain failure free survival for those that received PCI, however they observed some patients declined PCI due to patient or physician concerns related to toxicity and also patients older than 65 years of age were significantly less likely to receive PCI [23]. An updated study from the same institution showed PCI maintained its association with OS, even in the MRI era [24]. Another study from Memorial Sloan Kettering Cancer Center showed that patient concerns regarding neurotoxicity was the most cited reason for the omission of PCI. Karnofsky performance status and clinical AJCC stage were significantly associated with OS but not PCI in this retrospective study [25].

Given the associated side effects with PCI, its utility to manage LS-SCLC patients when MRI brain surveillance is available is being questioned. In addition to the retrospective studies highlighted above, some studies have shown no associated improvement in OS or PFS with PCI for LS-SCLC in the MRI era [19,26] while other studies do report an OS benefit with PCI [24,27]. Further prospective results from clinical trials that include LS-SCLC patients, such as the SWOG S1827 MAVERICK (SWOG S1827) trial comparing PCI to MR surveillance (NCT04155034), are awaited to provide modern prospective evidence.

Table 2. Various recent studies that detail the utility of PCI in LS-SCLC with study information and key findings.

Study and Publication Year	Total Cohort of SCLC Patients	SCLC Patients That Received PCI (*n*, % of Total Cohort)	Intervention vs. Control	Endpoints	Key Findings and Statistics (Intervention vs. Control)
Prospective Studies					
Aupérin et al., 1999 [18]	987	526 (53.2)	No PCI [ref] vs. PCI	OS Disease-free survival	Pooled relative risk of 0.84 (95% CI, 0.73–0.97) Pooled relative risk of 0.46 (95% CI, 0.38–0.57)
** Slotman et al., 2007 [28]	286	143 (50.0)	No PCI [ref] vs. PCI	Time to symptomatic brain metastases Cumulative risk of brain metastases within 1 year Disease-free survival 1-year survival	HR, 0.27 (95% CI, 0.16–0.44) 40.4% (95% CI, 32.1–48.6) vs. 14.6% (95% CI, 8.3–20.9) HR 0.76 (95% CI, 0.59–0.96) 13.3% (95% CI, 8.1–19.9) vs. 27.1% (95% CI, 19.4–35.5)
Redmond et al., 2017 [29]	20	20 (100.0)	Hippocampal-sparing PCI (no comparator)	HVLT-R delayed recall at 6 months after completion of PCI Reliable Change Index at 6 months for HVLT-R delayed recall Reliable Change Index at 12 months for HVLT-R delayed recall 2-year survival Median progression-free survival	7.06 (SD 2.77, n = 14) 17.6% 7.10% 88% (95% CI, 68–100%) Not reached
Levy et al., 2019 [30]	547	449 (82.0)	Secondary analysis of PCI in CONVERT study thoracic BID [ref] vs. once daily [6]	* Brain relapse times * Median OS 3-year survival	HR 0.95 (95% CI, 0.60–1.50) 28 months (95% CI, 22–35) vs. 31 months (95% CI, 27–52) 48% (95% CI, 41–55) vs. 42% (95% CI, 36–49)

Table 2. *Cont.*

Study and Publication Year	Total Cohort of SCLC Patients	SCLC Patients That Received PCI (*n*, % of Total Cohort)	Intervention vs. Control	Endpoints	Key Findings and Statistics (Intervention vs. Control)
Retrospective Studies					
Giuliani et al., 2010 [23]	228	127 (55.7)	PCI vs. no PCI	Brain FFS Median OS	76.6% (95%, CI, 68–87) vs. 46.7% (95% CI, 8–34) 21.7 months (95% CI, 17–36.8) vs. 11.2 (95% CI, 8.9–14.1)
Ozawa et al., 2015 [26]	124	29 (23.4)	PCI vs. no PCI (with MRI and SRS salvage)	* Median OS * Brain metastasis occurrence rates in 2 years	25 vs. 34 months 43.0% vs. 38.4%
Qiu et al., 2016 [31]	399	185 (46.4)	Early vs. late PCI	Symptomatic brain metastases at 6, 12 and 24 months 1-year OS rates 3-year OS rates	0, 3 and 13% vs. 7, 29 and 42% 96% vs. 82% 53% vs. 35%
Lok et al., 2017 [25]	208	115 (55.0)	PCI vs. no PCI (no significant difference in outcomes, all patients reported together)	Median OS 2-year OS rates 3-year OS rates	35.1 months 64% 49%
Farooqi et al., 2017 [32]	658	364 (55.3)	No PCI [ref] vs. PCI	Risk of death Risk of brain metastasis	HR 0.73 (95% CI 0.61–0.88) HR 0.56 (95% CI 0.40–0.78)
Wu et al., 2017 [22]	283	114 (41.0)	PCI vs. no PCI (no significant difference in outcomes, all patients reported together)	Median survival 2-year survival 5-year survival 2-year cumulative incidence of brain metastasis	26 months (95% CI, 22–34 months) 53% 33% 17%
Pezzi et al., 2020 [19]	297	205 (69.0)	No PCI [ref] vs. PCI	* OS * 3-year incidence rate of brain metastasis	HR 0.844 (95% CI, 0.604–1.180) 11.20% (95% CI, 5.40–19.20) vs. 20.40% (95% CI, 12.45–29.67)
Yan and Toh et al., 2021 [24]	369	196 (71.0)	PCI [ref] vs. no PCI	OS Brain failure risk	HR 1.77 (95% CI, 1.31–2.40) HR 2.93 (95% CI, 1.85–4.63)

* no significant difference. ** study in ES-SCLC patients.

3. Novel Radiation Approaches to Manage LS-SCLC

3.1. Intensity Modulated Radiation Therapy (IMRT)

While treatment options for LS-SCLC patients have not dramatically altered in the last 20 years, conformal radiation techniques have improved outcomes for patients and decreased treatment-related toxicity.

3.1.1. IMRT for Thoracic RT

Lower comformality with 2D RT and 3D conformal radiation therapy (3DCRT) increases the amount of the surrounding normal tissue that receives high dose RT. As such, there is a risk of developing higher rates of toxicities with 2D or 3DCRT such as esophagitis or pneumonitis as compared to IMRT [33].

A retrospective study from MD Anderson Cancer Center analyzed clinical records for 223 LS-SCLC patients treated from 2000 to 2009. 119 of these patients received 3DCRT while the remaining 104 patients received IMRT. The authors show that LS-SCLC patients who received IMRT required significantly fewer percutaneous feeding tube insertions compared to those who received 3DCRT (5% vs. 17%) but there were no differences in outcomes between these two techniques [33].

3.1.2. IMRT for Hippocampal-Avoidance PCI (HA-PCI)

Given a lack of a wide variety of treatment options, further investigation is warranted for PCI utility to find a balance between improving patient outcomes and quality of life through the reduction in treatment-related toxicity and disease control. With the advent of conformal RT techniques, such as IMRT or volumetric modulated arc therapy (VMAT), selective avoidance of brain sub-structures with potential for decreased neurotoxicity rates while maintaining disease control has become possible.

Accordingly, published in 2021, the PREMER clinical trial randomized 150 SCLC patients (107 limited-stage and 43 extensive-stage) and showed that HA-PCI, delivered by IMRT or VMAT, reduced the risk of worse delayed free recall (DFR) on the Free and Cued Selective Reminding Test (FCSRT) at 3 months without any significant difference in OS and brain metastases [34]. We also eagerly await the NRG CC003 study, which is planning to randomize up to 400 SCLC patients (LS and ES stage) to assess the 6-month deterioration in Hopkins Verbal Learning Test-Revised (HVLT-R) Delayed Recall associated with HA-PCI as compared to conventional PCI.

3.2. Stereotactic Body Radiation Therapy (SBRT)

Stereotactic body radiation therapy (SBRT) has been utilized for patients with stage I NSCLC [35–37]. There is limited evidence for the use of SBRT for LS-SCLC patients. Given that SCLC is generally considered to be more radiosensitive compared to NSCLC, the combination of SBRT and chemotherapy may be an option for the 5% of patients that present with clinical stage I SCLC, however evidence is currently sparse [35].

A single-institution retrospective study in 2013 reported eight inoperable LS-SCLC patients treated with SBRT and chemotherapy demonstrated this strategy as a safe and effective alternative. 3-year survival and disease-free survival rates were reported at 72% and 86%, respectively, with minimal toxicity [38]. Another small retrospective study in 2015 of six patients with stage I SCLC showed the use of SBRT to manage the primary tumour had 100% local control at year with no associated regional nodal failure and distant failure in the liver was reported in one patient. 1-year OS was at 63% and disease-free survival (DFS) was 75% [39]. A multi-institutional study across 24 institutions primarily evaluated the use of SBRT in T1-T2N0M0 SCLC patients and interrogated the benefit of chemotherapy. Adding chemotherapy to SBRT showed an OS benefit of 31.4 months in comparison to 14.3 months in the group without. DFS was 61.3 months in the group that received both chemotherapy and SBRT compared to 9 months without [40].

The National Comprehensive Cancer Network (NCCN) recommends the use of SBRT for stage I-IIA SCLC patients that do not undergo surgery. The strategy for SBRT mirrors

those for NSCLC based on NCCN recommendations [41]. In comparison to the UK's National Institute for Health and Care Excellence (NICE) guidance and the Cancer Care Ontario (CCO) guidelines, this recommendation is noticeably not present [42,43]. Due to lack of data, currently there are no known guidelines or recommendations regarding SBRT for the more advanced stages (i.e., IIB-IIIC) LS-SCLC. Further prospective studies are required to adequately determine efficacy of SBRT, optimal dose and fractionation, along with chemotherapy sequencing for the treatment of LS-SCLC patients.

3.3. Proton Beam Therapy

After correction of other prognostic factors, it has been shown for NSCLC patients that there is a correlation between radiation therapy doses to the heart and OS [44]. This has led to further evaluation of proton beam therapy to reduce doses of radiation to the heart while ensuring there is adequate delivery of radiation to the lung cancer. There has been emerging evidence for outcomes for LS-SCLC patients treated with proton beam therapy. A single-institution prospective study investigating outcomes for 30 LS-SCLC patients that received proton beam therapy showed a median OS of 28.2 months with limited incidence of high-grade toxicities [45]. While these results are encouraging, further evaluation is required in clinical trials.

3.4. Stereotactic Radiosurgery (SRS) and Whole-Brain Radiation Therapy (WBRT)

Though SCLC patients with brain metastases are considered ES-SCLC, stereotactic radiosurgery (SRS) is worth briefly reviewing. Whole brain RT (WBRT) remains the standard of care for SCLC patients with brain metastases and evidence for the routine use of SRS remains limited for SCLC. In 2004, the RTOG 9508 trial reported the outcomes of 331 cancer patients with a variety of disease sites and histologies (i.e., only 6–9% patients had small cell histology) randomized to receive WBRT alone with and without SRS boost and identified a OS advantage for patients with a single brain metastasis treated with WBRT and SRS boost [46]. Of note, a 2020 paper reported the First-line Radiosurgery for Small-Cell Lung Cancer (FIRE-SCLC) multi-institutional cohort study that retrospectively evaluated the outcomes of SRS in 710 SCLC patients [47]. Results from FIRE-SCLC comparing SRS showed a median OS of 8.5 month and the time to central nervous system progression (TCCP) was 8.1 months. For those with single brain metastasis, the median OS was 11 months and TCCP was 11.7 months [47]. These results suggest SRS could be an option for selected SCLC patients and further evaluation is prospective clinical trials are warranted for SCLC.

4. Novel Therapeutic Strategies for LS-SCLC

4.1. Targeted Therapies and Molecular Subtypes

The availability of high throughput next-generation genome sequencing technologies has allowed lung cancers to be molecularly profiled leading to the establishment of driver mutations contributing to tumour proliferation. For example, studies have shown that the epidermal growth factor receptor (*EGFR)* oncogene drives tumour growth and proliferation in NSCLC [48–55]. Immunotherapies targeting the programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis such as nivolumab, pembrolizumab, and atezolizumab have shown efficacy in NSCLC [56–59].

While targeted small molecule therapies are routinely considered in the management of NSCLC, these are not currently the mainstay of treatment for SCLC patients due to the lack of currently targetable oncogenes with sufficient prevalence in SCLC. Rather, SCLC's high mutational burden is suggested to be strongly associated with tobacco exposure with 98% of cases appearing in smokers [60]. New molecular pathways require further investigation to establish their roles in SCLC and also whether targeted treatments improve LS-SCLC patient outcomes. Candidate therapeutic targets in SCLC are challenging to identify given that prevalent mutations in SCLC are mainly loss of function with the involvement of tumour suppressor genes *RB1* and *TP53* [60].

4.1.1. DNA Damage Response Inhibitors (DDR)

As the inactivation of *RB1* and *TP53*, SCLC tumours exhibit increased susceptibility to DNA damage. Mediators in the DNA damage response (DDR) pathway, such as poly (ADP-ribose) polymerase (PARP), have been investigated as potential therapeutic targets [60,61].

Several studies have shown that a combination of DDR inhibitors with chemotherapy or other targeted treatments could be a potential option for SCLC patients [62,63]. SLFN11 has been suggested as a potential biomarker of sensitivity of DNA damage chemotherapy and PARP inhibition in SCLC [62,64–66]. After *RB1* and *TP53*, gene amplification of *MYC* is among the most common genetic abnormalities found in 20% of SCLCs [60]. A phase II clinical trial combining paclitaxel with or without alisertib, an aurora kinase A (AURKA) and AURKB inhibitor, showed slight improvement in PFS in a general SCLC patient population. However, subtype analysis showed doubling of PFS in patients with MYC-high SCLC tumours [67,68].

Lurbinectedin, an inhibitor of gene transcription and RNA polymerase II, received FDA approval in 2020 as a second-line treatment option for SCLC [69]. Topotecan was previously the only other option in the second-line setting but its use is limited due to toxicity concerns and modest efficacy [70–72]. A single-arm, phase II basket trial evaluated the efficacy of lurbinectedin in 105 SCLC patients that experienced recurrence or resistance to initial treatment. Overall response rate by investigator assessment was 35.2% and the rate of disease control was 68.6% [73]. The most common grade 3–4 adverse events reported in this phase II trial were anaemia (9%), leucopenia (29%), neutropenia (46%), and thrombocytopenia (7%) [73]. The most reported side effect associated with lurbinectedin was myelosuppression in the initial phase I trial in advanced solid tumours [74]. The toxicity profile of lurbinectedin may make its incorporation for LS-SCLC management challenging, especially with concurrent chemoradiotherapy.

4.1.2. Delta-like Protein 3 (DLL3)

Whole-genome sequencing analysis revealed inactivating mutations in the primary *NOTCH* family of genes in 25% of SCLC tumours [75]. Overexpression of a negative regulator of *NOTCH* signaling, delta-like protein 3 (DLL3), was found in a majority of SCLC patients [76]. An anti-DLL3 antibody-drug conjugate called rovalpituzumab teserine (Rova-T) showed antitumor activity when evaluated in a phase I clinical trial with patients who had recurrent SCLC [77] OS benefit [78–82].

However, DLL3 has remained of interest and has shown to act as a biomarker of sensitivity [76–78]. Results are awaited for an ongoing phase I clinical trial (NCT03319940) evaluating AMG 757, a half-life extended bispecific T-cell engager (BiTE) immunotherapy against DLL3 [83].

4.2. Immunotherapies

Successes in establishing the routine use of immunotherapies for SCLC patients had been limited [84,85]. In ES-SCLC, trials investigating the efficacy of immunotherapies including rilotumumab, ganitumab, and ipilimumab in combination with chemotherapy trials did not show significant OS benefit [86–89]. The landmark 2018 published study showed the addition of atezolizumab to chemotherapy in first-line treatment of ES-SCLC improved OS and progression-free survival (PFS) compared to chemotherapy alone [88]. In 2019, atezolizumab combined with carboplatin and etoposide received FDA approval based on the IMpower133 clinical trial for ES-SCLC.

Durvalumab combined with first-line chemotherapy is another treatment that showed significant OS benefit when treating ES-SCLC patients [90]. Pembrolizumab in addition to chemotherapy in the first line treatment of patients with ES-SCLC was shown to have prolonged OS in the Keynote-604 study (HR, 0.80; 95% CI, 0.64 to 0.98). However, a higher significance threshold was set in this study and was not achieved (p-value = 0.164) [91]. Despite ongoing study, there has yet to be well defined biomarkers that predict benefit from immune-checkpoint inhibitors [85], however one promising biomarker approach for

ES-SCLC reported by Gay et al. [92] leveraged the IMpower133 patient samples and defined an inflamed gene signature (SCLC-I) that correlated with atezolizumab benefit. This SCLC subtype had uniquely expressed genes that included numerous immune checkpoints and human leukocyte antigens in the absence of a transcriptional signature [92]. Whether this SCLC-I subtype in ES-SCLC would extend into LS-SCLC patients and associated treatment approaches remains unanswered.

Specific to LS-SCLC, a phase I/II trial published in 2020 investigated concurrent chemoradiation with pembrolizumab for LS-SCLC patients reported pembroluzimab was well tolerated. Patients were followed-up for a median time of 23.1 months with median PFS of 19.7 months. Median OS was reported to be 39.5 months [93]. However, other immunotherapies are being evaluated in randomized studies for LS-SCLC, such as the NRG LU0005 trial (NCT03811002), a phase II/III trial that is comparing concurrent atezolizumab with chemoradiation compared to chemoradiation alone and its effects on PFS and OS.

Unfortunately, the recent phase II STIMULI trial of 153 randomized LS-SCLC patients showed no improvement in PFS with the addition of consolidation nivolumab-ipilimumab following chemoradiation for LS-SCLC [94]. Another ongoing study is the ADRIATIC trial (NCT03703297) that is evaluating the effects of consolidation durvalumab and tremelimumab on the PFS and OS of LS-SCLC patients without progression following concurrent chemoradiation [95].

We eagerly await the results of these ongoing studies that will define the role for immunotherapy for LS-SCLC patients. Studies about ongoing and completed prospective studies for immunotherapies in LS-SCLC are summarized in Table 3.

Table 3. Ongoing and completed prospective studies for immunotherapies in LS-SCLC.

Study and Publication Year	Total Cohort of LS-SCLC Patients	Intervention	Endpoints	Key Findings and Statistics (Intervention vs. Control)
Completed Trials				
Welsh et al., 2020 [93]	40	Concurrent pembroluzimab	Maximum tolerated dose Median progression-free survival Median OS	No grade 5 toxicities, 3 grade 4 events (2 neutropenia, 1 respiratory failure). [n = 40] 19.7 months (95% CI, 8.8–30.5) [n = 40] 39.5 months (95% CI, 8.0–71.0) [n = 40]
Peters et al., 2021 [94]	153	Consolidation immunotherapy (nivolumab and ipilimumab) vs. observation after standard chemo-radiotherapy and PCI [ref]	* Progression-free survival * OS	HR 1.02 (95% CI, 0.66–1.58) HR 0.95 (95% CI, 0.59–1.52)
Ongoing Trials				
Senan et al., 2019 [95]	600 (estimated enrollment)	Consolidation durvalumab ± tremelimumab vs. placebo	Progression-free survival OS	Currently ongoing
Ross et al., 2020 [96]	506 (estimated enrollment)	Concurrent chemoradiation plus atezolizumab vs. chemoradiation	Progression-free survival OS	Currently ongoing

* no significant difference.

4.3. Pre-Clinical and Translational Studies

Efforts to define molecular subtypes of SCLC are ongoing. Gene expression profiling of SCLC from cell lines, patient tissue, and murine models have identified differential expression of transcriptional regulators (ASCL1, NEUROD1, POU2F3, YAP1, and ATOH1) or immune-related genes (SCLC-I) as candidate molecular subtypes [92,97,98].

5. Discussion

5.1. Current Limitations

The primary modality of LS-SCLC treatment remains concurrent chemoradiation with platinum-based chemotherapy [4,7]. Concurrent chemoradiation has long been established as the standard of care for LS-SCLC patients, particularly by two meta-analyses in 1992 showing this treatment modality improved OS and local disease control [8]. Turissi et al. [5] showed a significant difference in median survival for patients that received BID radiotherapy compared to those that received a once-daily regimen [5]. However, it is noted that the findings from the CONVERT trial suggested an increased dose of once-daily radiotherapy to 66 Gy did not show OS benefit compared to the 45 Gy/30 BID regimen [6]. Through collaborative decision-making with their physician, eligible patients without brain metastasis can undergo PCI which has been established by prospective studies to improve OS and reduce subsequent intracranial metastases [18].

There remain further controversies in the management of LS-SCLC. Optimal LS-SCLC radiation fractionation is still being debated between the benefits of the current recommended fractionation scheme and increasing it [5,6]. The role of PCI in the MRI era is being evaluated with the rationale for surveillance with MRI brain to lower PCI-related neurotoxicity in LS-SCLC patients while maintaining OS [20].

5.2. Risks and Benefits with Multi-Modal Combinatorial Therapies

Further consideration by clinicians is required to balance the risk and benefit of further treatment with studies increasingly investigating new targeted therapies and immunotherapies to treat SCLC patients. While the first-line of treatment for LS-SCLC patients remains concurrent chemoradiation, there is potential for further addition of novel combination or adjuvant therapies. For novel combination therapies with concurrent chemoradiation, caution needs to be exercised with respect to treatment tolerability, whereas additional adjuvant therapies may be more tolerable however may forgo potential concurrent treatment synergy. For example, prospective studies investigating the use of immunotherapy in both concurrent or consolidation following chemoradiation are underway to leverage the orthogonal mechanisms of action among each individual treatment and an acceptable toxicity profile [94,95].

5.3. Molecular Subtyping of SCLC Leading towards an Understanding of Inter- and Intra-Tumour Heterogeneity

SCLC is moving from being studied as a homogenous disease and towards being classified as a heterogenous disease (e.g., transcription factor subtypes: SCLC-A, SCLC-N, SCLC-P, SCLC-Y, SCLC-I, etc.) [97,98]. This distinction is crucial as a more comprehensive molecular definition of SCLC subtypes can help enable the discovery of biomarkers that suggest drug sensitivity or resistance and stratify patients according to their response to targeted therapies, the bedrock of precision medicine [99,100].

Single-cell RNA-sequencing (scRNA-seq) has enabled further exploration of inter- and intra-tumour heterogeneity, cell types, and cell states [101,102]. scRNA-seq technology is increasingly gaining higher throughput capabilities and sustainable cost, allowing a greater number of single-cells to be profiled at this resolution [102]. Bulk-sequencing technologies used to measure gene expression may not be able to capture the complete heterogeneity in a diverse biological system such as tumours; these technologies only measure the average expression levels of each gene in a large population of cells [103].

Further study using mouse and human models in combination with time-series analysis of scRNA-seq data has revealed MYC as a driver of dynamic evolution of SCLC subtypes [104]. It is suggested that MYC can convert SCLC subtypes in a context-specific manner; with the loss of *RB1* and *TP53*, MYC can promote a pulmonary neuroendocrine cell from SCLC-A to SCLC-N to SCLC-Y in vivo. This study suggests that intratumoural subtype heterogeneity is critical to be considered when designing future clinical trials [104].

Characterisation of generated circulating tumor cell (CTC)-derived xenografts from SCLC patients using scRNA-seq of chemosensitive and chemoresistant CTC-derived xenografts suggests increased intratumoral heterogeneity following therapy resistance. Multiple subsets of unique SCLC cells may develop within a tumour and there needs further consideration of diverse therapeutic strategies to maximize treatment response before the development of resistance mechanisms [105]. With the era of precision medicine well underway, SCLC patients have yet to have benefited from the promise of various targeted therapies. Subtype identification for SCLC has yielded promising targets that require further interrogation [97,98]. As SCLC moves towards being considered a heterogeneous disease, subtype identification may help select patients that may benefit maximally from a particular treatment and reduce the failure rate of clinical trials. With more SCLC subtypes being defined to enable precision medicine [97,98], it is also key for clinicians to consider how to effectively recruit for and design statistically sound clinical trials. However, it remains a challenge to find effective therapeutic strategies for LS-SCLC given a significant majority of studies are focused on ES-SCLC.

As the throughput of scRNA-seq technologies improve in parallel with falling costs, tumour heterogeneity can be further explored to reveal new subtypes of SCLC and their plasticity to deliver on the promise of precision medicine. More crucially, the integration and innovation with radiation in combination with chemotherapy and novel therapeutics represent the next frontier in managing LS-SCLC patients. While this remains an exciting prospect, prospective studies to carefully consider the benefit to LS-SCLC patients while managing tolerability will be necessary.

6. Conclusions

Novel treatment options for LS-SCLC patients remain promising but compartmentalized as a majority of novel treatments are tested first in ES-SCLC. The landscape of LS-SCLC can be transformed with the integration of new targeted therapeutics and immunotherapies to standard-of-care concurrent chemoradiation. Prospective studies are eagerly awaited to determine the routine use of PCI in the MRI era, novel radiation techniques such as HA-PCI, proton therapy, SRS, and SBRT, along with the ideal dose fractionation schedule for LS-SCLC patients. In order to capture tumour heterogeneity, scRNA-seq in addition to bulk sequencing technologies may improve SCLC subtype identification which may lead to biomarker-selected clinical trials. Despite the longstanding challenges with the management of LS-SCLC, novel approaches to treatment and biology are poised to bring much needed improvement to patient outcomes.

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