Review Article

Real-world treatment patterns and outcomes in small-cell lung cancer: a systematic literature review

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Background: Small-cell lung cancer (SCLC) accounts for 12–15% of lung cancers and is associated with poor survival outcomes and high symptom burden. This study employed a broad, systematic search strategy and timeframe to identify evidence on real-world treatment patterns and outcomes for SCLC outside the USA, including understanding sub-populations such as extensive-stage (ES) or limited-stage (LS) disease.

Methods: Databases (MEDLINE, Embase, and EBM reviews) were searched for journal articles published in the English language between 1 January 2000–1 March 2020 and supplemented by hand searching of conference abstracts and posters presented at conferences between 1 January 2016–1 March 2020 reporting real-world treatment outcomes in patients with SCLC. A targeted clinical guideline review was also completed.

Results: One-hundred studies provided quantitative data; 57 were available as full-text articles, whilst the remaining 43 were presented as abstracts or posters. The majority (80 studies, 80%) of included studies reported treatment in the first-line setting, where platinum-based chemotherapy and chemoradiotherapy was the most commonly used treatment strategy, in line with current treatment guidelines in SCLC. First-line treatments were found to have a high response rate; however, most patients relapsed early. No studies reported treatment or outcomes with immune-oncology therapies. Second-line treatment options were very limited, and primarily consisted of either re-treatment with first-line regimen or topotecan, but the prognosis for these patients remained poor. Outcomes were particularly poor amongst those with ES or relapsed disease *vs.* LS disease.

Conclusions: SCLC treatment patterns and short survival outcomes have remained constant over the previous 20 years. Due to the search timeframe, none of the studies identified reported on the impact of recently approved immune-oncology therapies in SCLC. Further data is needed on the impact of immunotherapies on treatment patterns and real-world outcomes in SCLC.

Keywords: Small-cell lung cancer (SCLC); systematic literature review; treatment patterns; treatment outcomes; survival; real-world

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Introduction

Approximately 10–15% of lung cancer cases are classified as small-cell lung cancer (SCLC), which is associated with an extremely poor rate of survival of 6.9% at 5 years from the point of diagnosis for the vast majority of patients (1). SCLC has a complex molecular pathogenesis with a high mutational burden and genomic instability, with SCLC patients commonly experiencing metastases, including brain metastases, which are present in around 10% of patients at diagnosis and developing in about 40–50% as the disease progresses (2).

Staging of SCLC has traditionally been performed

according to the Veterans Administration Lung Study Group (VALSG) two-stage method, which classifies SCLC into limited-stage (LS) disease (confined to the ipsilateral hemithorax and all known disease can be encompassed within a single radiation port) and extended-stage (ES) disease (disease in the contralateral hemithorax and distant metastases) disease (3). Recent staging projects have shown that tumour node metastasis (TNM) staging of SCLC (LS defined as absence of distant metastatic disease), combined with the VALSG method, provides more accurate prognoses and treatment options (4,5).

In comparison to non-SCLC, there have been limited therapeutic advances in the management of SCLC over the past 30 years. Topotecan was approved for the treatment of relapsed SCLC by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2007 and 2009, respectively. More recently, atezolizumab and durvalumab, immune checkpoint inhibitors, were approved in USA for first-line treatment in ES SCLC patients when used with etoposide plus either cisplatin or carboplatin (6,7). Consequently, given the lack of therapeutic developments, long-standing chemotherapies and radiotherapies are extensively used in the treatment of SCLC with limited success; median survival for patients with LS disease is currently 15–20 months, with 20–40% surviving to 2 years, and for those with ES disease, median survival is 8–13 months with 5% surviving to 2 years (8). Reports of prophylactic cranial irradiation (PCI) have shown a decrease in the incidence of brain metastases and some have shown an improvement in overall survival (OS) (9). Other notable agents in late-stage development include pembrolizumab, under evaluation in both first-line and relapsed SCLC (10-12).

A recent study by Povsic *et al.* assessed the real-world comparative effectiveness and tolerability of a defined set of SCLC treatments (immune-therapy, single-agent or combination chemotherapy, or radiotherapy) published between 2006–2018 (13). OS was found to be poor in SCLC and no treatment option included was found to be clearly superior. Furthermore, real-world treatment effectiveness and tolerability data were found to be fragmented and inconsistently reported, with available publications primarily of poor quality and lacking statistical analyses.

To our knowledge, no systematic exploration of the full SCLC treatment landscape has been previously published; with ongoing clinical research into novel options, there is value in mapping this landscape to understand the state of treatment options in this indication. Questions remain in the literature regarding the breadth of the SCLC treatment landscape, differential treatment patterns and outcomes for SCLC sub-populations, and the degree to which practices reflect clinical guidelines. In addition, previous reviews have largely focused on real-world treatment patterns from database registries in the USA, and hence there is a need to more closely review evidence from outside the USA.

In this review, we aimed to employ a broad, systematic search strategy and timeframe to explore treatment patterns and outcomes for SCLC in the real world outside the USA, including understanding sub-populations by stage (LS *vs.* ES), line of therapy, and prophylaxis for brain metastases. A targeted search was carried out to identify clinical guidelines globally (including the USA) to contextualise the results of the real-world treatment review. Real-world studies from the USA were excluded to pragmatically restrict an already broad search strategy.

We present the following article in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-3034).

Methods

Systematic literature review

A systematic review was conducted to identify publications reporting on real-world treatment patterns and outcomes in patients with SCLC. This review is reported in accordance with the PRISMA statement (14).

Eligibility criteria

The review included all observational studies published in English between January 2000 and March 2020 which provided quantitative data on the classification, clinical management, rates of treatment for adult patient outcomes in SCLC outside the USA, regardless of stage or type of disease. Clinical trials were excluded as they are based on treatment within a controlled setting and may not reflect current clinical practice. Furthermore, case studies and opinion pieces were also excluded from this review as they provided limited quantitative data on treatment patterns or treatment outcomes. Samples of general lung cancer patients were included if they reported on subgroup data specific to the SCLC population. Further information on study eligibility in terms of population, intervention(s), comparator(s), outcomes and study design (PICOS) is provided in *Table 1*.

Table 1 PICOS inclusion and exclusion criteria

Criterion	Inclusion criteria	Exclusion criteria
Population	• Adults diagnosed with small-cell lung cancer • No restrictions on gender, ethnicity, stage or type of disease	• Patients diagnosed with NSCLC • Paediatric patients • USA-only studies
Intervention	• All types of intervention used for the diagnosis and treatment of SCLC	N/A
Comparator	• All types of comparator for the diagnosis and treatment of SCLC	N/A
Outcome	• Treatment rates: – Treatment strategy (including adjunctive therapies) – Dosing (dosing, method of administration, no. of cycles used, on/off-label usage) – Adherence/persistence to therapy – Length of follow-up • Real-world clinical outcomes relating to the efficacy &/or safety, including: – Response rates – Overall survival/progression-free survival – Adverse events	• Data that only reports outcomes relating to: – PROs & HRQoL (to be captured as part of a separate review) – Costs & resource use, including: Cost effectiveness, price, societal costs – Carer burden – Pharmacokinetics
Study design	• Studies documenting real-world activity in SCLC, including: – Observational studies – Cohort studies – Cross-sectional studies – Case series and reports – Expert opinions – Physician surveys • Literature reviews (systematic and non-systematic)	• Randomised controlled trials • Network meta analyses • Studies documenting the treatment of SCLC patients based solely in USA treatment centres • Studies published pre-2000 • Not published in English • Animal studies • Nutritional studies • *In vitro* studies • Pharmacodynamic and pharmacokinetic studies

SCLC, small-cell lung cancer; PRO, patient-reported outcome; HRQoL, health-related quality of life.

Search strategy and information sources

Electronic databases (MEDLINE, Embase and EBM reviews) were searched systematically in December 2018, with searches reran in March 2020 to account for any newly published data (i.e., between January 2019 and March 2020). The search terms used in the Embase and MEDLINE databases are provided in Table S1 of the supplementary material. Notably, we did not pre-define the treatments of interest, but captured all therapies in the population of interest. Data on treatment patterns and/or outcomes not yet available in full manuscript form were identified through grey literature searches of posters and abstracts published at the following conferences between January 2016 and March 2020; ASCO, ESMO, ECC, WCLC, ALCC and JLCC. Furthermore, a bibliography review of all included studies was performed to capture any additional publications not identified throughout the core searches.

Data collection and extraction

All records identified in the searches were screened independently by two reviewers against eligibility criteria for full-text review with discrepancies resolved with the aid of a third independent reviewer. Data extraction from full texts was performed independently in duplicate. Information on study design, patient characteristics, outcomes, and conclusions was extracted from each full text or congress abstract. If congress posters were retrievable, data were extracted from the poster, if not, data were extracted from the abstract.

Data analysis

A qualitative synthesis of the evidence was completed and is described in a narrative summary in the results. Quantitative analyses or meta-analyses were not undertaken in this review.

Risk of bias assessment

As no quantitative synthesis was performed, and due to the limited methodological information reported in the included congress abstracts, no quality assessment checklist was deemed relevant to the range of outcomes reported.

Protocol

The study protocol for this review was not registered.

Targeted search for guidelines

Supplemental targeted online searches of European and North American professional society and guideline agency websites were conducted in December 2018 and March 2020. The searches sought to identify any clinical guidelines or consensus statements on the diagnosis, staging or treatment of SCLC.

Results

Study selection

Across both the December 2018 and March 2020 searches of bibliographic databases, conference publications and other web-based resources, 6,465 unique records were identified. After the screening process, 272 records were reviewed as full texts or congress abstracts. One-hundred records, all reporting observational studies, were included (*Figure 1*).

Study characteristics

Table 2 summarises the characteristics of the 100 observational studies, of which 57 were full text articles and 43 congress abstracts or posters (full results available in Table S2 of the supplementary material). All but one record were of unique retrospective studies (99%), with one prospective tracking study (1%). Studies had a broad geographic spread: coming from Europe (25%), Asia-Pacific (56%), North America and South America (10%), and the Middle East, Turkey, and North Africa (7%). The majority of studies were published in the last twelve years (97%), and three (3%) studies before 2008.

Patient characteristics

Most studies reported on patients undergoing first-line treatments (80%), with 17 studies (17%) following patients in second and subsequent lines of therapy, and, a further 3 studies (3%) assessing treatment of secondary brain metastases in SCLC patients (*Table 3*). Eighteen studies reported treatment of patients with LS, 14 of patients with ES, and the remaining 30 of patients at a variety of stages. A further 16 and 2 studies reported on PCI and maintenance therapies following induction chemotherapy in first-line SCLC, respectively. Twenty-six studies reported disease functioning scales, most commonly the ECOG performance status (15-30), or the Karnofsky performance status (31-36).

Demographics of patients from the quantitative studies matched the SCLC patient profile described in the literature (37), whereby patients are likely to be male and over 50 years of age. In the 62 studies reporting age, the average patient age was over 50 years (medians between 55 and 75), and in 83% of studies reporting age, over 60 years. Males comprised a larger proportion within study cohorts in all but one study (38). Twenty-four studies reported the smoking status or smoking history of their cohorts. In most studies (n=23) that reported smoking status, current smokers and former smokers comprised the majority of the cohort. Twenty-seven studies reported rates of brain metastases in their cohort prior to treatment, but this varied between study, ranging from 0% (39) to 64% (40), with the typical cohort comprising 10–30% of patients with brain metastases (n=18).

Treatment patterns: first-line

Limited stage

Fifty-three records reporting on first-line treatment included LS SCLC patient cohorts: with 46 studies reporting use of chemotherapy, either alone or in combination with thoracic radiotherapy. In 36 studies, a majority of patients received a chemotherapy regimen of etoposide, combined with platinum-based treatment, most typically for 4–6 cycles. The remaining patients in these studies received either PCDE (cisplatin, cyclophosphamide, doxorubicin, etoposide), PEI (cisplatin, etoposide, ifosfamide), CAV (cyclophosphamide, doxorubicin, vincristine), cyclophosphamide or amrubicin regimens. A slight preference of cisplatin was found over carboplatin in studies which included patients who had received a platinum-based regimen (15,41-47). Surgical resection followed by chemotherapy or chemoradiotherapy was used in 4 studies, in which all patients had either stage I or stage II disease under the TNM classification system.

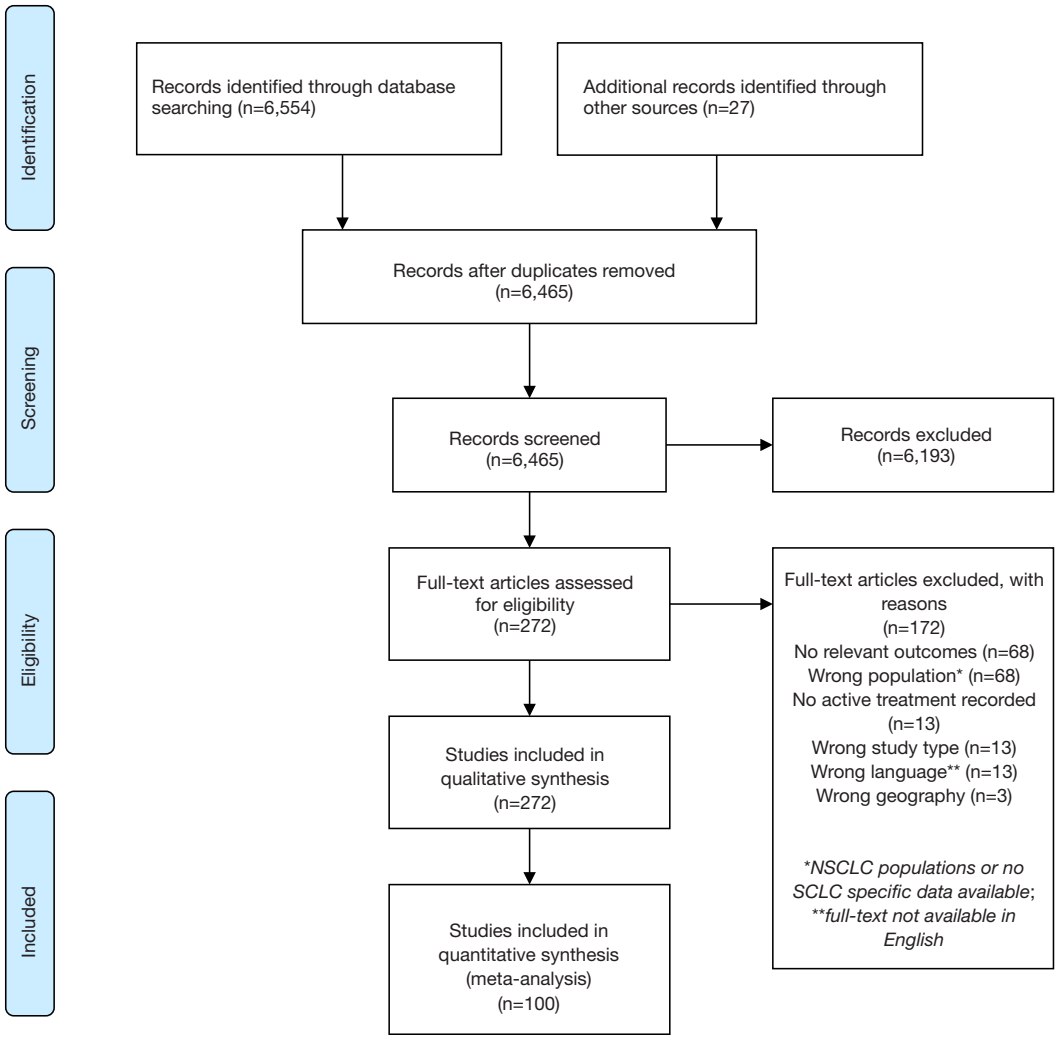


Figure 1 PRISMA flow diagram.

Extensive stage

Eleven studies were identified specific to ES patients in the first-line setting (18,31,32,36,48-55). No studies reported use of immunotherapy agents. Instead, all reported patients were treated with either chemotherapy or chemoradiotherapy. Of those that provided the exact chemotherapy regimen, all reported a platinum-based therapy combined with etoposide. Most studies did not report a preference for either cisplatin or carboplatin. However, of the 3 studies which reported a majority of patients receiving cisplatin, 2 were from China and 1 from Thailand (32,36,52,55). Chemoradiotherapy was reported in five of twelve studies specific to first line in ES SCLC (31,32,36,48,51). The proportion of the radiotherapy uptake in those studies ranged from 44.5–61% (31,48).

PCI

Thirty-four studies reported patients being treated with PCI, 16 in which all patients were treated with PCI as the main intervention in the study. PCI was used less frequently among ES patients [range 1.6%–12.4% of patients, 4 studies (31,32,35,51)] compared with LS [range, 33–61.5% of patients, 10 studies (16,29,41,42,44,45,56-59)]. Uptake of PCI amongst mixed intervention cohorts ranged between 1.6% and 61.5% (36,60).

Treatment patterns: relapsed/refractory disease

Seventeen studies (21,23,24,28,40,61-70) reported on the treatment of SCLC patients beyond first-line treatment. Patients were either retreated with their first-

Table 2 Characteristics (study and patient) of the included studies

Characteristics of records	N (%)
No. of studies included in final analysis	100
Publication type	
Full journal articles	57 (57%)
Congress abstracts	43 (43%)
Year of publication	
2013–present	70 (70%)
2008–2013	27 (27%)
Pre–2008	3 (3%)
Type of study	
Retrospective	100 (100%)
Country/continent	
International	2 (2%)
Europe	25 (25%)
Denmark	2
France	2
Germany	5
Netherlands	1
Poland	2
Portugal	1
Serbia	1
Slovakia	1
Slovenia	2
Spain	4
UK	4
Asia	56 (56%)
Australia	1
China	24
India	1
Japan	24
Korea	2
New Zealand	1
Singapore	1
Thailand	2
META	7 (7%)
Egypt	1
Israel	1
Turkey	4
Tunisia	1
America	10 (10%)
Canada	8
Brazil	2
Stage of disease/intervention*	
LS-SCLC (surgery)	4 (4%)
LS-SCLC (CT/CRT)	14 (14%)
ES-SCLC (CT/CRT)	14 (14%)
All 1st line patients (LS-SCLC and ES-SCLC)	28 (28%)
PCI	16 (16%)
Treatment of secondary brain metastases	3 (3%)
Maintenance therapy	3 (3%)
Relapse or refractory disease	17 (17%)

*Not all studies are mutually exclusive with some reporting treatment patterns or outcomes in multiple SCLC populations. CT, chemotherapy; CRT, chemoradiotherapy; ES, extensive stage; LS, limited stage; META, Middle East, Turkey and Africa; PCI, prophylactic cranial irradiation; SCLC, small cell lung cancer.

line platinum chemotherapy regimen, a topoisomerase inhibitor (either irinotecan, topotecan, or amrubicin) [11 studies, (21,24,29,61-67,71,72)], or paclitaxel [6 studies (23,28,65,73-75)].

A single study included LS SCLC patients in second and subsequent lines of treatment (40). Fourteen patients in the Aktas *et al.* study were treated sequentially with irinotecan followed by topotecan while 11 patients received topotecan followed by irinotecan.

Treatment outcomes

Limited stage

Patients who underwent surgery had comparatively high

Table 3 Clinical guidelines providing recommendations for the diagnosis, staging or treatment of small cell lung cancer

Agency	Title of guideline	Jurisdiction	Year of publication	Guideline coverage	
				Diagnosis	Treatment
ESMO	SCLC: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (Fruh *et al.*, 2013, Jett *et al.*, 2013)	Europe	2013	✓	✓
ACCP	Diagnosis and Management of Lung Cancer, 3rd ed: ACCP Evidence-Based Clinical Practice Guidelines (Jett *et al.*, 2013)	USA	2013	✓	
ASCO	Treatment of Small-Cell Lung Cancer: ASCO Endorsement of the ACCP Guideline (Rudin *et al.*, 2016)	USA	2015	✓	
NCCN	NCCN Clinical Practice Guidelines in Oncology: Small Cell Lung Cancer (Kalemkerian *et al.*, 2018)	USA	2016	✓	✓
BTS	Guidelines on the Radical Management of Patients with Lung Cancer (Lim *et al.*, 2010)	UK	2010	✓	
NICE	Lung cancer: diagnosis and management (Baldwin *et al.*, 2011)	UK (England & Wales)	2011	✓	✓
SIGN	SIGN 137: Management of Lung Cancer [(SIGN), 2014]	Scotland	2014	✓	✓
SEOM	SEOM clinical guidelines for the treatment of small-cell lung cancer (Domine Gomez *et al.*, 2013)	Spain	2013	✓	
HSE	Diagnosis, staging and treatment of patients with lung cancer: National Clinical Guideline No. 16 (Executive, 2017)	Ireland	2017	✓	✓
Alberta Health Services	Clinical Practice Guideline LU-006: Small Cell Lung Cancer: Limited Stage (Services, 2012a)	Canada	2012	×	✓
Alberta Health Services	Clinical Practice Guideline LU-007: Small Cell Lung Cancer: Extensive Stage (Services, 2012b)	Canada	2012	×	✓
Cancer Care Ontario	Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy (Ontario, 2017)	Canada	2017	✓	✓
Cancer Care Ontario	Chemotherapy for Relapsed Small Cell Lung Cancer (Ontario, 2013)	Canada	2013	✓	
Cancer Care Ontario	Prophylactic Cranial Irradiation in Small Cell Lung Cancer (Ontario, 2003)	Canada	2003	×	✓

✓=included in recommendations; × =not included in recommendations. ACCP, American College of Chest Physicians; ASCO, American Society of Clinical Oncology, BTS=British Thoracic Society; ESMO, European Society for Medical Oncology, HSE=Health Service Executive; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; SCLC, small lung cell cancer; SEOM, Spanish Society for Medical Oncology; SIGN, Scottish Intercollegiate Network.

OS averages, with median OS ranging between 20.4 and 89 months [6 studies (33,44,56,76-79); *Figure 2A*]; use of surgery was confined to a very small subset of patients with LS disease, which may explain the higher OS values.

In LS patients undergoing chemotherapy and chemoradiotherapy treatments [14 studies, (15,29,41-45,47,55,57,60,68,69,80)], median OS rates ranged from between 13.9 and 41.1 months [*Figure 2B*, (29,45,55,57,60,68,80)]. Thoracic radiotherapy delivered concurrently with chemotherapy produced favourable OS rates compared with when delivered subsequently [median OS 29.7 *vs.* 22.6 months (80), Median OS 41.1 *vs.* 38.1 months (45), 5yr OS 27.3% *vs.* 11.7% (44), respectively]. No study reported the OS of patients treated with radiotherapy alone. Some studies (42,45,69) commented on the higher rates of toxicity amongst those patients administered with higher doses.

Sixteen studies (20,34,35,38,39,55,56,70,81-88) reported LS patients undergoing PCI (*Figure 2C*). The impact of PCI in improving survival *vs.* patients who did not receive PCI was mixed, with some studies demonstrating an OS/progression-free survival (PFS) improvement [8 studies (20,34,35,38,39,83,85,86)], whilst others showing no improvement or a reduced OS [3 studies (82,84,88)]. However, all but one (88) studies that reported on the incidence of brain metastases found the addition of PCI led to a reduction in incidence [7 studies (20,34,35,39,81,87,89)].

Extensive stage

In all studies reporting OS in ES SCLC patients receiving first-line treatment, median OS was below 2 years, with median OS ranging between 5.9–18 months [12 studies (18,31,32,36,48-55); *Figure 2D*]. Amongst those patients who received platinum-based chemotherapy alone in the first-line setting, median OS ranged from 9.3–13 months (18,49,50,52-54). The median PFS in ES SCLC following first-line treatment [10 studies (18,31,32,36,48-52,54)] was 5–10 months. In the 2nd and 3rd line settings [17 studies (21,23,24,28,40,61-67,71-75)], both PFS and OS were considerably shorter (PFS 1.5–8.2 months; OS see *Figure 2E*).

Clinical guidelines in SCLC

The targeted search of electronic database and online sources identified 14 relevant clinical guidelines from 11 professional bodies which provided recommendations on the diagnosis, staging or treatment of SCLC (*Table 2*). In Canada, the regional based agencies for Alberta and Ontario published guidelines separately for the management of SCLC by stage of disease (LS & ES) and line of therapy (1L, PCI, R/R), respectively.

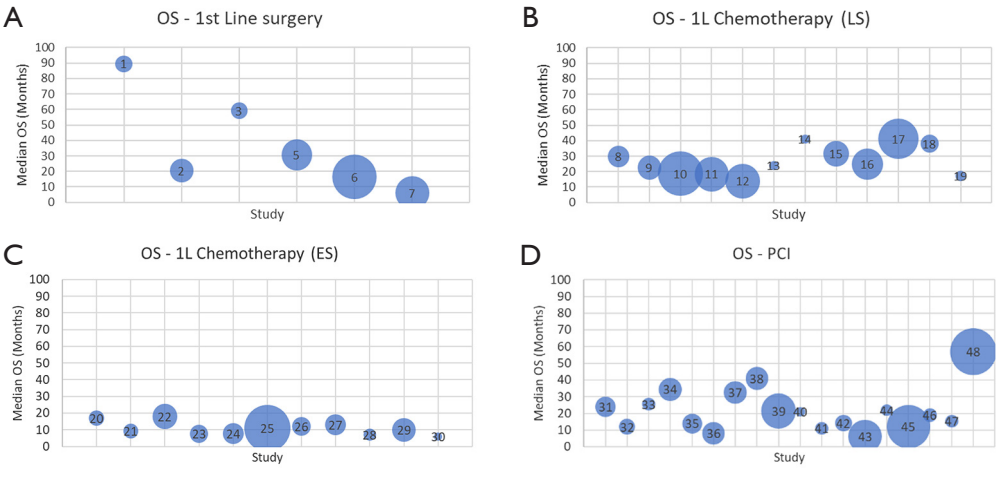
Overall, there was a high degree of alignment between the published guidelines. In the first-line setting, all agencies recommended treatment with platinum-based chemotherapy plus etoposide for a period of 4–6 cycles in both LS and ES patients. In LS disease, guidelines indicate that treatment is aimed to be curative, with surgery and thoracic radiotherapy considered as treatments to be used alongside platinum chemotherapy. All published clinical guidelines identified in this review recommended the use of concurrent chemoradiotherapy (with or without prior surgical resection) for first-line LS patients. In ES disease, additional treatment beyond platinum chemotherapy was limited to radiotherapy, however, the recommendations within this patient population were mixed, with most guidelines providing no specific recommendation or confining use to sequential radiotherapy for the palliation of patient symptoms. PCI was recommended as an option for both LS and ES patients if they had managed to achieve stable disease following initial treatment and had a good performance score using a validated metric (for example, ECOG score).

Amongst patients who did not respond to therapy or experienced an early relapse, clinical guidance notes that prognosis is poor and often recommends palliative management focused upon reducing tumour size—this is commonly recommended through best supportive care or clinical trials. In the case of a treatment-free interval of 3–6 months, guidelines recommend the use of topotecan or re-treatment with the patient's first-line platinum chemotherapy regimen.

Discussion

Treatment patterns

This study employed a broad, systematic approach to exploring treatment patterns and outcomes for SCLC in the real world, with a focus on understanding sub-populations by stage, line of therapy and PCI use. Clinical practice appears to be highly aligned with existing treatment guidelines in SCLC, brought about by the lack of therapeutic developments over the time frames of the included studies, driving consensus amongst the clinical



1 Ploenes *et al.* (surgery+neoadjuvant)
2 Ploenes *et al.* (surgery)
3 Ogawa *et al.*
5 Zhang *et al.* (surgical)
6 Zhang *et al.* (non-surgical)
7 Bagshaw *et al.* (surgery)
8 Dong *et al.* (concurrent chemoradiotherapy)
9 Dong *et al.* (sequential chemoradiotherapy)
10 Hermes *et al.* (1-4 cycles)
11 Hermes *et al.* (5-6 cycles)
12 Aynaci *et al.*
13 Matsuura *et al.* (45 GY)
14 Matsuura *et al.* (54 GY)
15 Chen *et al.* (concurrent chemoradiotherapy)
16 Chen *et al.* (non-concurrent chemoradtiotherapy)
17 O Hara *et al.* (concurrent chemoradiotherapy)
18 O Hara *et al.* (sequential chemoradiotherapy)
19 Sukauichai *et al.*
20 Zhu *et al.* (chemoradiotherapy)
21 Zhu *et al.* (chemotherapy)
22 Luan *et al.*
23 Mellemgaard *et al.* (Etoposide oral)
24 Mellemgaard *et al.* (Etoposide IV)
25 Sallam *et al.* (4 cycles)
26 Sallam *et al.* (>4 cycles)
27 Sedef *et al.*
28 Shirasawa *et al.* (with interstitial pneumonia)
29 Shirasawa *et al.* (without interstitial pneumonia)
30 Sukauichai *et al.*
31 Ramlov *et al.* (Limited Stage)
32 Ramlov *et al.* (Extensive Stage)
33 Ozawa *et al.* (PCI)
34 Ozawa *et al.* (No PCI)
35 Bang *et al.* (PCI)
36 Bang *et al.* (No PCI)
37 Qui *et al.* (Early PCI)
38 Qui *et al.* (Late PCI)
39 Qui *et al.* (No PCI)
40 Matutino *et al.* (PCI)
41 Matutino *et al.* (No PCI)
42 Srivastava *et al.* (PCI)
43 Srivastava *et al.* (No PCI)
44 Stanic *et al.* (PCI)
45 Stanic *et al.* (No PCI)
46 Boskovic *et al.* (PCI)
47 Boskovic *et al.* (No PCI)
48 Liu *et al.* (Limited Stage)
49 Asai *et al.*
50 Inomata *et al.*
51 Morise *et al.*
52 Murakami *et al.* (Re-challenge)
53 Murakami *et al.* (AMR)
54 Aktas *et al.* (IRI/TOP)
55 Aktas *et al.* (TOP/IRI)
56 Granados *et al.*
57 Itotani *et al.*
58 Minemura *et al.* (Sensitive relapse)
59 Minemura *et al.* (Refractory relapse)
60 Zhang *et al.* (PE+IRO)
61 Zhang *et al.* (TOP)
62 von Eiff *et al.*
63 Shufei *et al.* (IRO+NED)
64 Shufei *et al.* (IRO+P)
65 Sone *et al.*
66 Wang *et al.* (IRO+PE)
67 Wang *et al.* (TOP)
68 Saijo *et al.* (Relapsed)
69 Moharana *et al.* (Recurrent)
70 Sugiyama *et al.*
71 Zhao *et al.* (IRI)
72 Zhao *et al.* (TOP)
73 Zhao *et al.* (PTX)
74 Zhao *et al.* (DTX)

Figure 2 Median rates of overall survival from each study stratified by study cohort. (A) Median overall survival in studies assessing first-line surgical interventions in small-cell lung cancer*. (B) Median overall survival in studies assessing first-line chemotherapy interventions in extensive stage small-cell lung cancer*. (C) Median overall survival in studies assessing first-line chemotherapy interventions in extensive stage small-cell lung cancer*. (D) Median overall survival in studies assessing prophylactic cranial irradiation in small-cell lung cancer*. (E) Median overall survival in studies assessing second-and third-line chemotherapy interventions in extensive stage small-cell lung cancer*. *The size of each bubble is representative of the study's sample size.

community. None of the included studies captured real-world data for the use or outcomes of durvalumab or atezolizumab, which are expected to become the future standards of care for first-line ES-SCLC.

Among first-line LS patients, chemoradiotherapy consisting of once or twice daily thoracic radiotherapy with etoposide plus either cisplatin or carboplatin is the standard of care treatment. Concurrent chemoradiotherapy has been shown in earlier studies to provide improved outcomes relative to sequential treatment (90,91). Thus, guidelines and current clinical practice show that sequential chemoradiotherapy is limited to a small subset of LS patients who are unable to tolerate an intensive combined regimen (for example, elderly patients or those with a poorer performance status). We identified limited uptake of surgery within the published data, which is most likely explained by SCLC being an aggressive disease which usually presents in advanced forms at the point of diagnosis, thus limiting the potential pool of patients who could be eligible for resection.

In ES patients, the progression of the disease limits treatment options. As a result, the standard of care is platinum-based chemotherapy with etoposide, which was the reported therapeutic strategy in >80% of first-line ES patients. There was a slight preference for the use of cisplatin over carboplatin, which produces better survival outcomes but is associated with a more unfavourable adverse event profile (92). This suggests that mostly younger, fitter patients were being enrolled onto active treatment, in line with the clinical guidelines. Thoracic radiotherapy has limited uptake when compared to the LS population, with almost all ES-patients who received chemoradiotherapy receiving it sequentially, and, usually only for the palliation of symptoms. Due to most real-world studies containing both ES SCLC and LS SCLC patients, and, not always providing subgroup data, it remains difficult to accurately estimate the scale of uptake for chemoradiotherapy in ES SCLC. However, a high volume of ES SCLC specific studies only included patients who had received chemotherapy, suggesting chemoradiotherapy has a limited role in ES disease.

The published literature reports a high response rate to first-line treatment (approx. 70%), however, patient relapse is frequent and rapid (93). Despite a high proportion of patients requiring 2nd line (and 3rd line treatment), there was a limited number of studies which reported on treatment patterns and/or outcomes for this population. This could suggest that most patients who relapse or are refractory to first-line treatment have a poor medical prognosis and thus may not be considered fit enough to undergo active treatment (94). Among the published studies in the relapsed setting, we found a consistency between the guidelines and current practice, with most patients receiving either a topoisomerase inhibitor (irinotecan or topotecan) or retreatment with their previous first-line chemotherapy regimen. In older patients, usually defined as those over 70 years of age, we found a preference for enrolment onto amrubicin, which was not always explicitly recommended in the published treatment guidelines.

Treatment outcomes

The review confirmed the limitations of current therapeutic approaches in SCLC for all but small subset of patients. In LS disease, surgical resection followed by adjuvant chemotherapy provided the best outcomes, with high rates of survival reported at 5 years for all but one study. Concurrent chemoradiotherapy was also an effective option; with studies reporting a high degree of patients surviving beyond 2 years. However, these treatment options are only considered appropriate for the estimated 30% of SCLC patients who present with LS disease at diagnosis. In the remaining 70% of SCLC patients with ES disease, treatment outcomes are notably poorer. Platinum-based chemotherapy delivers high initial response rates, however, most patients relapse early, contributing to a median survival which rarely exceeded 12 months for the studies we identified in this review. Second-line treatment options primarily consist of either re-treatment with a patients first-line regimen or topotecan, but the prognosis for these patients remains poor with most studies reporting a median OS of between 4 and 8 months.

The findings from our review with respect to treatment outcomes were aligned with a previous, more targeted, review of effectiveness of individual therapies (13). This was also confirmed by a systematic review of randomised controlled trials by Cope *et al.* for a range of different treatments across all stages of SCLC (95). Our results further highlight that poor outcomes are particularly evident amongst those with ES *vs.* LS disease, including both those who undergo surgical resection or receive chemoradiotherapy. Second- and third-line treatment options were seen to have limited effect in ES patients, contributing to limited uptake of active treatment and poor survival outcomes in this population. There is a clear unmet need for new treatment options which could delay the time

to relapse in first-line patients or improve survival outcomes for those patients in relapsed and remission settings. In recent clinical studies, both atezolizumab and durvalumab have demonstrated improvements in median OS of 2.0- and 2.7-month *vs.* platinum chemotherapy alone in first-line ES-SCLC patients, respectively. The availability of these new options could pave the way for a higher durability of response, and, in turn, survival (6,7).

PCI

We examined studies exploring PCI as a sub-set of interest. Because the blood–brain barrier restricts the penetration of most chemotherapeutic agents into the brain, leaving the brain a susceptible site for relapse, PCI is considered in patients who have responded to therapy; however, because most ES patients are in a poor medical state, PCI is often not considered appropriate. Based on this review, uptake of PCI in this population is approximately 10–20%. Furthermore, the clinical benefit of PCI is unclear, particularly in the ES population. Most studies of first-line ES disease explored the efficacy of platinum-based chemotherapy, and although all studies included a cohort of patients who subsequently received PCI, no subgroup analyses of these patients were performed. Therefore, only a limited number of real-world studies which specifically examined the impact of adjuvant PCI could be used. These studies demonstrated that PCI resulted in significant reductions in the incidence of brain metastases compared with patients who did not undergo PCI. However, a reduction in brain metastases did not necessarily translate to a survival benefit, with studies presenting varied results. This finding is aligned with a recent systematic review of PCI, which concluded that, although data appeared to show PCI improved survival, this may be confounded by issues such as whether brain imaging had been used to confirm presence of brain metastases (96).

Gaps in the literature

Several data gaps were identified in this review. One area with a paucity of data was in the second-line treatment of SCLC patients. Those studies that did have a cohort of second-line patients show the role of second-line treatments is usually palliative with an emphasis on extending life and reducing symptom burden. In addition, there were limited studies focussed on patients with ES and relapsed disease. Furthermore, those studies that did report in these subgroups were typically small single-centre studies, from disparate geographic settings.

Study limitations

This study had some methodological limitations. Firstly, our analysis of current management in the USA was limited to guidelines only; the primary reason for this was to pragmatically restrict an already extremely broad search (with the USA anticipated to have a high volume of literature). However, our review found a high degree of alignment between treatment guidelines, irrespective of country. Furthermore, we found no differences in clinical practice between countries using real-world data. Therefore, we believe that current treatment in the USA will align to their respective guidelines. Secondly, only real-world data was identified from studies published in the literature and our search strategy did not involve specific database or registry searches. However, given the large volume of studies which were identified as congress abstracts, which included a number of small single-centre chart reviews or database analyses, we believe that most sources of data will have been captured in our review.

Thirdly, our analysis was strictly qualitative with no quantitative synthesis being performed. This was the aim—given the amount of heterogeneity between studies, a quantitative analysis would have considerable uncertainty and necessitate a more restrictive search strategy. Finally, the review did not incorporate an assessment of study quality using a validated questionnaire or survey as our analysis was limited to a qualitative exploration of treatment patterns and outcomes and did not include any quantitative evidence syntheses. Furthermore, as a number of studies identified in this review were congress abstracts, they had limited information on study methods, meaning it would be difficult to complete any assessment of study quality using standard instruments.

Conclusions

To our knowledge, this is the broadest systematic search of real-world treatment patterns and outcomes in SCLC. SCLC has poor survival outcomes, particularly in patients with ES disease. Treatment practices are well-aligned to clinical guidelines, which partly reflects the limited options available to treat SCLC. Consequently, outcomes have not considerably improved during at least the last twenty years. Furthermore, although PCI is recommended by

guidelines and has been shown to have clinical benefit, the impact on OS is questionable and it may be unsuitable for patients with poor performance status (such as those with ES disease). Although a wide variety of study designs were identified, there was a paucity of data in second and subsequent lines of therapy, and in ES disease patients specifically. This review highlights a need for more efficacious treatments to mitigate the burden of disease. There is also a need for longitudinal and patient-centred studies with treatment-specific results, to better explore the disease- and treatment-related burden on patients and to better understand the long-term survival rates of patients with SCLC. The impact of upcoming new standards of care, such as durvalumab and atezolizumab, also needs to be assessed as more data become available.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Search terms used in the Embase databases (search strings adapted for compatibility with other databases)

#	Search terms (Embase & Medline)
1	small cell lung cancer'/exp
2	small cell carcinoma'/exp
3	'sclc'
4	(pancoast* OR 'superior sulcus' OR 'pulmonary sulcus') NEXT/4 (tumo?r* OR syndrome*)
5	(small OR oat OR reserve OR round) NEXT/1 'cell' NEXT/1 (lung* OR pulmonary OR bronch*) NEXT/3 (cancer* OR neoplasm* OR carcinoma* OR tumo?r* OR lymphoma* OR metast* OR malignan* OR blastoma* OR carcinogen* OR adenocarcinoma* OR angiosarcoma* OR chrondosarcoma* OR sarcoma* OR teratoma* OR microcytic*)
6	1-5 (or)
7	Observational.tw
8	(retrospective NEXT/1 study).tw
9	(prospective NEXT/1 study).tw
10	(chart NEXT/1 review).tw
11	(expanded NEXT/1 access NEXT/1 program).tw
12	7-11 (OR)
13	6 AND 12
14	Humans/lim
15	EM 2000/01

truncated term - finds variant word endings e.g., child finds child, childhood, children

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Table S2 Treatments and outcomes reported in the included studies

Author	Year	Country	Patient characteristics	Treatment received	Regimen	Outcomes	Conclusion
Surgery							
Ploenes *et al.*	2012	Germany	No. of patients = 29 Mean age, years = 62 (46–82) Gender (male) = 75.9%	Surgery = 100%	Surgery and CT [neoadjuvant] = 52% Surgery and CT [Adjuvant] = 48%	OS (median) = 89.4mo (surgery +neoadjuvant) 20.4mo (surgery)	Surgical resection could be beneficial in highly selected patients [cT1-2 cN0 cM0 disease] who can be completely resected. Adjuvant therapy is recommended following surgery
Ogawa *et al.*	2012	Japan	No. of patients = 15 Mean age, years = 64 (54–77) Gender (male) = 92%	Surgery = 32.7% Induction CT = 33% Adjuvant CT = 82%	Induction CT = 100% [PE] Adjuvant CT = 76.9% [PE] Other = 23.1%	OS (median) = 59.2mo	N/A
Zheng *et al.*	2013	China	No. of patients = 54 Mean age, years = 56 (32–76) Gender (male) = 72%	Surgery = 66.6% [Radical resection]; 33.3% [Non-radical resection] Pre-operative chemotherapy = 42.6%	N/A	OS (5yrs) = 73% [Radical resection and pre-op chemo]; 27% [Radical resection and no pre-op chemo]; 67% [Non-radical resection and pre-op chemo]; 67%[Non-radical resection and no pre-op chemo]	Pulmonary resection could improve survival for patients with early LS-SCLC. Systemic chemotherapy is recommended for all SCLC patients
Zhang *et al.*	2014	China	No. of patients = 153 Mean age, years = 56 (23–84) Gender (male) = 73.2%	Surgery = 32.7% CT = 100% RDT = 56% PCI = 50%	Surgery and CT = 78% [adjuvant] 22% [neoadjuvant]	OS (median) = 30.5mo (surgical) 16.5mo (non-surgical)	Pulmonary resection could improve the survival for I–IIIA stage SCLC. Systemic therapy is recommended for all patients with SCLC.
Bagshaw *et al.*	2019	USA	No. of patients = 59	Surgery = 100%	Stereotactic radiosurgery = 100%	OS (median) = 6.2mo	Patients with SCLC treated with SRS appear to have similar rates of local failure, distant failure, and neurologic death compared to historical controls of SRS for non-SCLC
Cifarelli *et al.*	2019	International	No. of patients = 232 Age (median) = 63 Gender (Male,%) = 50.5%	Surgery = 100%	Gamma knife radiosurgery = 100%	OS (1yr) = 28%; Local failure (1yr) = 31%; Distant brain failure (1yr) = 49%	SRS plays an important role in the management of brain metastases from SCLC, especially in salvage therapy following WBRT
Chemotherapy/Chemoradiotherapy – Limited Stage							
Scepanovic *et al.*	2010	Slovakia	No. of patients = 81 Median age, years = 57 Gender (male) = 80%	CCRT = 100%	CT [PE = 100%; Minimum = 4 cycles] RDT [44 Gy in 22 fractions = 50% ; 54–64 Gy in 27 to 32 fractions = 50%]	OS (1yr) = 98% (44Gy group), 100% (54-64 Gy group) PFS (1yr) = 42% (44Gy group), 65% (54-64 Gy group) OS (2yrs) = 5% (44Gy group), 53% (54-64 Gy group) PFS (2yrs) = 2% (44Gy group), 20% (54-64 Gy group)	Higher RDT doses resulted in improved time to progression and survival
Tada *et al.*	2010	Japan	No. of patients = 30 Gender (male) = 80%	CCRT = 100% PCI = 33.3%	CT [PE = 46%; PEI = 27%; PCE=17%; CE = 10%] RDT [45Gy in 30 fractions = 100%]	CR = 83% OS (2yrs) = 54% OS (5yrs) = 26%	N/A

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

Author	Year	Country	Patient characteristics	Treatment received	Regimen	Outcomes	Conclusion
Dong *et al.*	2011	China	No. of patients = 166	CCRT = 29.5% SCRT = 37.3% CT = 33.2%	CT [CE/PE = 100%] RDT [Mean = 49.6 Gy]	ORR = 89.4% (CCRT), 67.2% (SCRT), 66% (CT) OS (median) = 29.7mo (CCRT), 22.6 mo (SCRT), 19.5 mo (CT) PFS (median) = 12.7mo (CCRT), 10.8mo (SCRT), 10.8mo (CT)	Chemoradiotherapy produce superior survival outcomes to CT alone. Similarly, CCRT results in increased survival vs SCRT
Hermes *et al.*	2011	Germany	No. of patients = 155 Median age, years = 63	CT= 100%	CT [CE = 100%]	Median OS = 18.7 mo (1–4 cycles) 18.5mo (5–6 cycles)	No. of cycles has limited impact on survival for patients with LS disease
Wzietek *et al.*	2011	Poland	No. of patients = 456	CCRT = 100% PCI = 37%	CT [PE = 100%] RDT dosing a) <45Gy b) 45Gy c) 45–54Gy d) >54Gy [No patient numbers provided]	OS (1yrs) = 5% (<45Gy); 25% (45Gy), 12% (45–54Gy), 15% (>54Gy)	Higher dose TRT doses failed to show any survival advantage compared with standard doses (e.g. 45Gy)
Morimoto *et al.*	2014	Japan	No. of patients = 81	CCRT = 100%	CT [CE = 19% ; PE = 81%] RDT [45Gy in 30 fractions = 100%; Median overall treatment time = 24 days	N/A	N/A
Aynaci *et al.*	2016	Turkey	No. of patients = 129 Mean age, years = 60.1 Gender (male) = 96.9	CCRT = 8% SCRT = 76% PCI = 31.2%	CT [CE = 89%; CAV = 6.9] RDT [>50Gy = 50%]	OS (median) = 13.9mo DFS (median) = 18mo	CCRT and >50Gy provide an improved OS/DFS over SCRT
Matsuura *et al.*	2016	Japan	No. of patients = 19	CCRT = 100%	CT [CE or PE - no. of patients not stated] RDT [45 Gy in 30 fractions = 47.3%; 54 Gy in 36 fractions = 52.8%]	Median OS = 24 mo (45 Gy group), 41mo (54 Gy group) OS (3yrs) = 33.3% (45 Gy group), 60% (54 Gy group) PFS (3yrs) = 0% (45 Gy group), 40% (54 Gy group)	CCRT with 54 Gy results in slower time to progression and improved survival without increased toxicity, compared to 45 Gy
Chen *et al.*	2016	China	No. of patients = 177 Gender (male) = 87%	CCCT =100% CCRT = 100% Followed by consolidation CT = 40.6% PCI = 61.5%	CT (induction) [PE = 100%] RDT = 100%] Consolidation CT [TOP = 60%; Other = 40%]	PFS (Median) = 17mo (CCRT), 12.9mo (non-CCT) OS (Median) = 31.6mo (CCRT), 24.8mo (non-CCT)	Consolidation CT can improve survival outcomes following initial treatment with CCRT
Sas-Korczyńska *et al.*	2017	Poland	No. of patients = 217 Mean age, years = 60.3 Gender (male) = 65%	CCRT = 46.5% SCRT = 53.5% PCI = 60.4%	CT [PE = 100%; Mean no. of cycles = 4.9] RDT [TRT dose = 40-66]	DFS (5yrs) = 28% mo (CCRT); 14.3% (SCRT); OS (5yrs) = 27.3% (CCRT); 11.7% (SCRT)	CCRT leads to improved survival outcomes, delayed thoracic reoccurrence and reduced distant metastases vs SCRT
Chen *et al.*	2018	China	No. of patients = 118	HFRT = 48.3% CFRT = 51.7%		OS (5yrs) = 26%(HFRT), 24% (CFRT) PFS (5yrs) = 22% (HFRT), 22% (CFRT)	HFRT and CFRT produce similar survival outcomes. HFRT was associated with reduced toxicities

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

Author	Year	Country	Patient characteristics	Treatment received	Regimen	Outcomes	Conclusion
O Hara *et al.*	2018	Japan	No. of patients = 254 Mean age, years = 64 Gender (male) = 77.1%	CCRT = 61% SCRT = 12% CT = 16% PCI = 38.5%	CT [CE = 22.8%; PE = 54.7%%] RDT [45 GY in 1.5 fractions twice a day = 62.8% ; 50 Gy in 25 fractions = 18.5%; No RDT = 16%}	Complete tumour response = 35% (CCRT); 18% (SCRT); 11% (CT) OS (Median) = 41.1 mo (CCRT); 38.1mo (SCRT); 15.6mo (CT) OS (5yrs) = 41% (CCRT); 36% (SCRT); 15.4% (CT)	SCRT produce comparable treatment outcomes to CCRT
Sukauichai *et al.*	2019	Thailand	No. of patients = 35 Age (median) = 61 Gender (Male,%) = 83%	CT = 80% PCI = 3%	CT [PE=51.4%; CE=28.7%]	OS (Median) = 17.7mo (LS), 5.9mo (ES)	The OS of the limited stage SCLC patients at our hospital was comparable to landmark studies. Most received sequential chemoradiation treatment
Matsuura *et al.*	2019	Japan	No. of patients = 13	CCRT = 100%	CT [PE/CE=100%] RDT [54Gy in 36 fractions in 18 days=100%]	OS (1yr) = 100%; OS (2yrs) = 92.3%; OS (3yrs) = 72.5%; PFS (1yr) = 76.9%; PFS (2yrs) = 53.9%; PFS (3yrs) = 53.9%	AHF-TRT of 54 Gy with concurrent PE or CE regimens resulted in a better OS and PFS without an increase in the severity of toxicity
Chemotherapy/Chemoradiotherapy – Extensive stage							
Zhu *et al.*	2011	China	No. of patients = 119 Mean age, years = 61 Gender (male) = 80.7%	CT = 49.6% CRT = 50.4% PCI = 1.6%	CT [PE = 87.4%; CE = 12.6%] CRT = 40-60Gy PCI = 1.6%	OS (median) = 17mo (CRT), 9.3mo (CT) OS (2yr) = 35% (CRT), 17% (CT) OS (5yr) = 7.1% (CRT), 5.1% (CT)	TRT added to CT improved OS in ES-SCLC patients.
Forde *et al.*	2012	UK	No. of patients = 81	CT = 39% SCRT = 61%	Not available	N/A	N/A
Luan *et al.*	2015	China	No. of patients = 167 Mean age, years = 59 Gender (male) = 82.6%	CT = 50.1% CCRT = 49.1% PCI = 2.9%	CT [PE= 77%; CE= 23%]	OS (median) = 18mo (CCRT), 12mo (CT) PFS (median) = 9mo (CCRT), 6mo (CT) OS (2yrs) = 35.3% (CCRT), 14.5% (CT) OS (5yrs) = 2.4% (CCRT), 2.4% (CT)	TRT added to CT improved OS in ES-SCLC patients.
Kim *et al.*	2017	Korea	No. of patients = 88 Mean age, years = 71 [65–83] Gender (male) = 82%	CT=100%	CT [etoposide-based regimen = 100%]	N/A	N/A
Li-Ming *et al.*	2017	China	No. of patients = 306 Mean age, years = 60 Gender (male) = 72%	CT = 55.5% CCRT = 44.5% PCI = 8.8%	CT [etoposide-based regimen = 100%]	OS (2yrs) = 21.4% (CCRT), 10.3% (CT) PFS (2yrs) = 7.7% (CCRT), 4.6% (CT)	TRT added to CT improved OS in ES-SCLC patients. High TRT doses improved OS over lower doses
Mellemgaard *et al.*	2017	Denmark	No. of patients = 200	CT = 100%	CT [oral etoposide= 42%; IV etoposide= 58%]	OS (median) = 227 days (etoposide oral), 235 days (etoposide IV) PFS (median) = 140 days (etoposide oral), 195 days(etoposide IV)	IV and oral produced similar OS but longer PFS with the IV schedule for ES-SCLC

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

Author	Year	Country	Patient characteristics	Treatment received	Regimen	Outcomes	Conclusion
Elegbede *et al.*	2018	Canada	No. of patients = 242 Mean age, years = 68	CT = 40% CRT = 60% PCI = 12.4%	Not available	N/A	In contrast to advanced NSCLC, systemic treatment uptake was high. However, <20% of patients followed through with PCI
Sallam *et al.*	2018	UK	No. of patients = 671	CT =100%	[CE=94%; PE=6%] Platinum + E (4 cycles) = 86%; Platinum + E (>4 cycles) = 14%	OS (median) = 11mo [4 cycles], 12mo [>4cycles] PFS (median) = 8mo [4 cycles], 9mo [>4cycles]	There is a lack of clinical benefit by extending first-line platinum combination treatment beyond four cycles in selected patients. This supports limiting the number of cycles to four until the superiority of a longer regimen is identified in a randomized study.
Sedef *et al.*	2019	Turkey	No. of patients = 117 Age (median) = 61 Gender (Male,%) = 90%	CT=100%	CT [PE/CE=100%]	OS (median) = 13mo PFS (median) = 8mo	Complete response and recurrent free time were the prognostic factors for ES SCLC patients in our study
Shirasawa *et al.*	2019	Japan	No. of patients = 161 Age (median) = 72 Gender (Male,%) = 85%	CT=100%	Not available	OS (median) w/ interstitial pneumonia = 7.1mo, PFS (median) w/out intertitial pneumonia = 10.0mo	Systemic chemotherapy was effective even in ED-SCLC patients with IP
Sukauichai *et al.*	2019	Thailand	No. of patients = 35 Age (median) = 61 Gender (Male,%) = 83%	CT = 80% PCI = 3%	CT [PE=51.4%; CE=28.7%]	OS (Median) = 5.9mo (ES)	The OS of the limited stage SCLC patients at our hospital was comparable to landmark studies. Most received sequential chemoradiation treatment
Mixed treatment cohorts							
Demeter *et al.*	2003	Canada	No. of patients = 100 Gender (male) = 75% Mean age, years = 61.9 Stage of disease = 33% [LS] 67% [ES]	CT= [LS = 86%; ES=64%] CRT= [LS = 83%; oES=63%]	Not available	OS (2yrs) = 22% [LS], 4% [ES]	N/A
Debevec *et al.*	2005	Slovenia	No. of patients= 51 Stage of disease = 47% [LS] 53% [ES]	Not available	Not available	OS (1yr) = 45% [LS], 10% [ES] OS (5yr) = 0%	N/A
Thammakumpee *et al.*	2007	Thailand	No. of patients = 116 Mean age, years = 63 (42–87) Gender (male) = 93% Stage of disease = 42% [LS], 58% [ES]	CT = 26% CRT= 28% RT= 20% BSC= 26%	PE = 97% (of CT/CRT patients)	OS (1yr) = 41% [LS], 22.4% [ES] OS (2yr) = 12.5%[LS], 3% [ES]	Response to chemotherapy was about 50% and median survival was significantly better than in patients without chemotherapy for both limited- and extensive-stage patients.
Sugiyama *et al.*	2007	Japan	No. of patients= 94 Mean age, years = 66 Gender (male) = 83% Stage of disease = 44.7% [LS], 55.3% [ES]	CT=100%	PE = 60% CE = 21% Other = 19%	Not available	N/A

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

Author	Year	Country	Patient characteristics	Treatment received	Regimen	Outcomes	Conclusion
Duarte *et al.*	2008	Brazil	No. of patients= 62 Mean age, years = 60.6 Gender (male) = 71.2% Stage of disease = 59% [LS]; 41% [ES]	CT=100%	PE = 69% CE= 31%	Not available	N/A
Li *et al.*	2009	China	No. of patients = 126 Age group, years = 84 [<70], 42 [>70] Gender (male) = 69% Stage of disease = 49% [LS], 51% [ES]	CT=100%	PE = 65.8% CAV = 34.2%	OS (median) = 13mo [<70], 12mo [>70] PFS (median) = 8mo [<70], 7mo [>70]	SCLC patients 70 years or older may tolerate and benefit from standard chemotherapy regimens (EP or CAV) with or without RT
Noguchi *et al.*	2010	Japan	No. of patients = 83 Age group, years = 38 [70-79], 45 [>80] Gender (Male, %) = 68% Stage of disease = 70% [LS], 30% [ES]	CT = 38.6% CRT= 25.3% RT= 4.8% BSC= 31.3%	Not available	OS (median, ES) = 9.2mo [70–79], 10.3mo [>80] OS (2yrs, ES) = 28% [70–79], 17% [>80]	Combination chemotherapy with or without TRT is feasible for patients aged 80 years with SCLC with PS 0 to 1, and even those with PS 2 to 3 or moderate comorbidities can benefit from these treatments
Devbhandari *et al.*	2010	UK	No. of patients= 67			OS (5yr) = 18% [LS = 33%, ES = 3%]	N/A
Garcia Prim *et al.*	2010	Spain	No. of patients= 98			OS (2yr) = 26.4% OS (median) = 8.83mo [LS]; 8.43mo [ES]	N/A
Nakao *et al.*	2010	Japan	No. of patients = 30 Age group, years = 35% [<70], 55% [>70] Stage of disease = 35% [LS], 55%[ES]	CT =100%	AMR = 100%	OS (median) = 301 days PFS (median) = 86 days	N/A
Lebau *et al.*	2011	France	No. of patients= 239 Mean age, years = 61 (50–72) Gender (Male, %) = 71% Stage of disease = 54.3% [LS], 45.7% [ES]	CT = 100%	PCDE = 44% PE = 32% Other = 24%	Complete response = 56% [PCDE]; 26% [PE] Objective response = 75% [PCDE]; 40% [PE]	N/A
Hermes *et al.*	2012	Germany	No. of SCLC patients = 397 Mean age, years = 63 [LS-SCLC] 61 [ES-SCLC] Stage of disease = 39% [LS]; 61% [ES]	CT = 28% [LS-SCLC], 95% [ES-SCLC] CCRT = 72% [LS-SCLC], 5% [ES-SCLC] PCI = 33% [LS-SCLC],22% [ES-SCLC]	CE = 98.1% [LS], 81.4% [ES] PE = 1.7% [LS], 6.1% [ES] Other CT = 0.2% [LS], 12.5% [ES]	OS (median) = 18.6mo [LS], 8.7mo [ES] PFS (median) = 7.2mo [LS], 3.55mo [ES]	N/A
Fisher *et al.*	2012	Canada	No. of patients= 171 Age group, years = 111 [75-79], 60 [>80] Gender (male) = 56.7% Stage of disease = 23% [LS]; 77% [ES]	CT = 100%	PE = 47% CE = 31% Oral etoposide = 21%	Outcomes presented as univariable and multivariable analyses	Elderly patients who are able to initiate chemotherapy are able to tolerate treatment and receive survival benefits from it

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

Author	Year	Country	Patient characteristics	Treatment received	Regimen	Outcomes	Conclusion
Molina-Guillen *et al.*	2012	Spain	No. of patients = 40 Mean age, years = 65.3 Gender (male) = 90% Stage of disease = 37.5% [LS], 62.5% [ES]	CT = 100%	Platinum based (CE or PE) =100%	PFI >6mo (ES patients) = 28%	Platinum based chemotherapy has been shown to be more effective in SCLC patients when they start the treatment at LS disease than ES. The 73.3% of the patients diagnosed and treated at the LS had a PFI longer than 6 months. However, only 28% of the patients who started the treatment at the ES reached a PFI longer than 6 months
Fujitani *et al.*	2013	Japan	No. of patients = 42 Mean age, years = 69 Gender (male) = 85.7% Stage of disease = 26.2% [LS]; 73.8% [ES]	CT = 100%	PE = 73.8% PC = 26.2%	OS (median) = 391 days [PE] Not reached [PC]	Physicians preferred PE for older patients as first-line therapy Survival outcomes tended to be better longer in the PC group
Postmus *et al.*	2013	Western Europe, Eastern Europe and Korea	No. of patients= 507 Mean age, years = 65.4 Gender (male) = 73% Stage of disease = 34% [LS], 66% [ES]	CT = 59% CRT= 67% [LS only] PCI = 26% [LS = 34%, ED=22%]	CT (first line) PE = 90.7%; CAV = 3.9%; CYC =3.9%; Other =2.5%]	OS (median) = 10.6mo [all patients]; 17.8mo [LS]; 8.7mo [ES]	The combination of platinum and etoposide remains first choice of chemotherapy at first line and often at relapse, followed by topotecan starting from second-line and beyond.
Islam *et al.*	2015	Australia	No. of patients = 41 Age group, years = 100% (>70) Stage of disease= 22% [LS], 78% [ES]	CT = 78% [All ES patients] CRT= 22% [All LS patients] PCI = 26% [LS = 34%, ED=22%]	Not available	OS (median) = 355 days [LS], 310 [ES] PFS (median) = 204 days [LS], 155 days [ES]	Elderly patients can be treated with standard doublet chemotherapy; however, dose reductions are required for a significant number of patients
Li *et al.*	2016	China	No. of patients= 77 Stage of disease = 42.7% [LS], 55.3% [ES]	Untreated = [LS = 32.4%; ES=47.6%] CT= [LS = 38.2%; ES=47.6%] CRT= [LS = 29.4%; ES=2.4%]	Not available	OS (median) = 14.23mo [LS], 12.5mo [ES]	N/A
Al Farsi *et al.*	2017	Canada	No. of patients= 185 Mean age, years = 64 Gender (male) = 50% Stage of disease = 37% [LS], 63% [ES]	CT = 51% CRT= 49% PCI= 43.2% [LS=64% , ES=39%]	PE = 53% CE= 47%	Incidence of relapse = 73% Time to relapse = 9.2mo [LS = 14.3mo, ES = 7.5mo]	<50% of eligible SCLC patients receive PCI. CNS relapse occurs frequently and more commonly in patients who do not receive PCI. Implementation of PCI in routine clinical practice appears to influence patterns of recurrence.
Silva *et al.*	2017	Portugal	No. of patients= 144 Mean age, years = 65 [42–87] Gender (male) = 79.9% Stage of disease= 25% [LS], 75% [ES]	CT = 100%	PE = 95.1%	ORR = 64% OS (median) = 5.5mo	Clinical practice at the centre represented that presented in the current literature. New treatments and predictive biomarkers for SCLC are urgently needed

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

Author	Year	Country	Patient characteristics	Treatment received	Regimen	Outcomes	Conclusion
Zhou *et al.*	2017	China	No. of patients = 523 Median age, years = 59 [27–87] Gender (male) = 79.3% Stage of disease = 26.8% [LS]; 73.2% [ES]	CT = 50.9% [LS = 39.3%, ES=55.1%] CRT= 49.1% [LS = 60.7, ES=44.9%] PCI = 12.6% [LS = 23.6%, ES = 8.6%]	All patients received either PE, CE, C+IRI or P +IRI	OS (median) = 21mo [LS] 13mo [ES] Other outcomes present as univariable and multivariable analyses	Limited stage disease and good response to initial therapy predicted a better survival for SCLC patients
Aquin *et al.*	2018	Canada	No. of patients = 531 Stage of disease = 30.2% [LS], 69.8% [ES]	CT=100%	PE = 73.8% CE = 26.2%	OS (median) = 322 days [PE] 224days [CE] Other outcomes present as univariable and multivariable analyses	Carboplatin appears to be an equally effective treatment option for SCLC, facilitating equivalent survival while avoiding toxicity
El Benna *et al.*	2018	Tunisia	No. of patient s= 60 Mean age, years = 61 [±6.5] Gender (male) = 95% Stage of disease = 33.3% [LS], 66.7% [ES]	CT=100%	CE/PE = 85%; Other =15%	N/A	Patients with SCLC are highly responsive to chemotherapy and radiation therapy. Long-term prognosis remains poor, with relapse and disease recurrence occurring in almost all cases
Hong *et al.*	2018	China	No. of patients= 999 Age group, years = 61.3% [<60], 38.7% [>60] Gender (male) = 69.3% Stage of disease = 59.1% [LS], 40.9% [ES]	Surgery +CRT = 5.9% [LS = 9.9%;] CT = 55.1% [LS = 52.5%, ES = 56.8%] CRT= 33.5% [LS = 33.2, ES = 32.8%]	PE = 89.3% [LS = 88.8%, ES = 90.1%] Non-PE = 10.7% [LS = 11.2%, ES = 9.9%]	OS (1yr) = 50.5% [LS], 32.2% [ES] OS (2yr) = 14.5%[LS], 8.7% [ES] OS (3yr) = 3.1% [LS], 2.6% [ES]	Several factors, including patient, tumour, and treatment characteristics and serum LDH levels are independent prognostic factors for OS and PFS in Chinese patients with SCLC
Lattuca-Truc *et al.*	2018	France	No. of patients= 529 Median age, years = 64 Gender (male) = 77% Stage of disease = 42% [LS], 58% [ES]	CT = 35% CRT= 65% PCI = [1997-09 = 26%, 2009-19= 32%]	Platinum based (CE or PE) =96%	Median OS = 12mo [1997-09=13mo, 2009-17= 11mo]	Since 1997 there was no improvement in survival nor response rate to chemotherapy in SCLC patients. There is a desperate need for new approaches in this setting
Saber *et al.*	2018	Egypt	No. of patients= 24	CT = 84%	PE/CE =100%	OS (median) = 7.7mo PFS (median) = 5.4mo	N/A
Cramer-Van Der Welle *et al.*	2019	Netherlands	No. of patients= 501 Age (mean) = 66 Gender (Male,%) = 67% Stage of disease = 100%[ES]	CT = 100%	Not available	OS (median) = 7.4mo	After first line systemic treatment in ED SCLC the fraction of patients receiving subsequent lines of treatment is rapidly decreasing
Incanc *et al.*	2019	Turkey	No. of patients= 177 Age (mean) = 56 Gender (Male,%) = 91% Stage of disease = 41% [LS]; 59%[ES]	CT = 100%	PE = 100%	Not available	We evaluated the relationship between NLR and SCLC, and found that NLR is a potential prognostic serum marker in patients with SCLC
Chemotherapy/Chemoradiotherapy 2nd/3rd line – Extensive stage							
Asai *et al.*	2012	Japan	No. of patients= 36 [second-line = 12%, third-line = 88%] Mean age, years= 69 [47–83] Gender (male) = 89% Prior therapies [CE= 62%, PE = 25%, other = 13%]	CT	AMR = 100%	OS (median) = 5.1mo PFS (median) = 2.9mo	AMR has the potential to be effective tool for the treatment of elderly patients (i.e. >70 years) with R/R SCLC

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

Author	Year	Country	Patient characteristics	Treatment received	Regimen	Outcomes	Conclusion
Inomata *et al.*	2014	Japan	No. of patients= 19 Mean age, years = 68 [47–78] Gender (male) = 94.7% Prior therapies [first-line platinum = 100%; second-line re-challenged platinum = 57.1%]	CT	Platinum doublet = 15.7% AMR = 47.4% TOP = 21% IRI = 10.4% PTX = 5.2%	OS (median) = 8.5mo	Numerous prognostic factors identified for improved OS in third-line SCLC
Morise *et al.*	2014	Japan	No. of patients= 57 Mean age, years = 70 [51–83] Gender (male) = 91% Prior therapies [PE = 47%, CE = 46%, RDT = 42, PCI = 23%]	CT	IRI=100%	ORR = 32% OS (median) = 5.3mo PFS (median) = 2.9mo	Low dose IRI has the potential to be an effective option for third-line SCLC with favourable toxicity
Murakami *et al.*	2015	Japan	No. of patients= 39 Mean age, years = 68 Gender (male) = 87.2%	CT	Re-challenge (existing platinum) = 33.3% AMR = 51.2% Other= 15.5%	OS (median) = 44.2mo [re-challenge], 20.9mo [AMR] PFS (median) = 8.2mo [re-challenge], 4.9mo [AMR]	Platinum re-challenge therapy provide better outcomes than single agent chemotherapy for relapsed SCLC
Aktas *et al.*	2016	Turkey	No. of ES-SCLC patients = 255 No. of ES-SCLC patients receiving second-line therapy = 117 [primary resistant = 17%, platinum sensitive = 83%] No. of ES-SCLC patients receiving third-line therapy = 25 [primary resistant = 12%, platinum sensitive = 88%] Mean age, years= 57 [39–74] Gender (Male,%) = 92%	CT (second-line and third-line regimen provided)	IRI/TOP = 44% TOP/IRI = 56%	OS (median) = 18mo [IRI/TOP], 14mo [TOP/IRI] PFS (median) = 14wks [IRI/TOP], 12wks [TOP/IRI]	Sequential monotherapy of TOP and IRI provide a considerable contribution to OS but sequencing of treatment provides similar outcomes
Granados *et al.*	2017	Spain	No. of patients= 83 Mean age, years = 58 [43–81] Gender (male) = 83.2% Prior therapies [CE= 38.7%, PE = 60.3%]	CT	PTX+GCB = 100%	OS (median) = 172 days PFS (median) = 148 days Treatment cessation (toxicity) = 14.4%	PTX+GCB is a well-tolerated regimen for relapsed SCLC and contributes to OS and PFS
Itotani *et al.*	2017	Japan	No. of patients= 21 Mean age, years = 70 [±5.6] Gender (male) = 85.7% ILD = 100%	CT	C+PTX =100%	OS (median) = 7.1mo PFS (median) = 3.5mo	In previously treated SCLC patients with ILD who had received more than one cytotoxic chemotherapy regimen, C+PTX is an effective treatment regimen
Minemura *et al.*	2017	Japan	No. of patients = 86 Mean age, years = 74 [70–84] Stage of disease = 48% [sensitive relapse], 52% [refractory relapse]	CT	AMR = 100%	OS (median) = 7.6mo [sensitive relapse], 5.5mo [refractory relapse] PFS (median) = 4mo [sensitive relapse], 2.7mo [refractory relapse]	Amrubicin demonstrated anti-tumour activity in both sensitive and refractory relapsed SCLC patients

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

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Yu *et al.*	2017	Japan	No. of patients= 54	CT	IRO+NED = 63% IRO+P = 37%	OS (median) = 62wks (IRO+NED), 58wks (IRO+P) PFS (median) = 23wks (IRO+NED), 19wks (IRO+P)	Irinotecan plus platinum is effective and tolerable for refractory and relapsed small cell lung cancer
Wang *et al.*	2017	China	No. of patients= 82	CT	IRO+PE = 54% TOP = 46%	OS (median) = 16.3 (IRO+PE), 10.1mo (TOP) PFS (median) = 6.2 (IRO+NED), 4.1 (IRO+P)	Combined chemotherapy with PEI is not inferior to topotecan monotherapy at second-line treatment
Zhang *et al.*	2018	China	No. of patients= 78	CT	P+E+IRO = 15.7% TOP = 47.4%	OS (median) = 16.3mo [PE+IRO] 13.1mo [66]	Combination chemotherapy with C+E+IRO could be considered as a second-line treatment option in patients with relapsed sensitive SCLC
von Eiff *et al.*	2018	Germany	No. of patients= 185 Mean age, years = 64 Gender (male) = 64.3% Prior therapies = 100% [CE/PE]	CT	PTX = 100%	OS (median) = 100 days PFS (median) = 48 days	Patients in good condition and without cerebral/hepatic metastases benefit from PTX therapy in relapsed SCLC
Saijo *et al.*	2019	Japan	No. of patients= 17 Gender (Male,%) = 71.1%	CT	PTX = 44.7%	OS (median) = 2.7mo; PFS (median) = 3.6mo	Although PTX-containing regimens demonstrated promising anti-tumor activity against relapsed SCLC with IIPs, the survival benefit was limited because of the high incidence of PTX-related AE of IIPs and treatment-related death
Moharana *et al.*	2019	India	No. of patients= 12	CT	PTX/IRI = 100%	PFS (median) 1.5mo	Weekly Paclitaxel in 2nd line may have favourable toxicity profile and response rate comparable to Irinotecan or Temozolomide
Moser	2019	Israel	No. of patients= 235 Age (median) = 64 Gender (Male,%) = 61% Prior therapies= 100%[PE]	CT	Not available	OS (median) = 11.8m	Overall survival for SCLC patients in a real world setting was found to be similar to those reported in clinical trials
Sugiyama *et al.*	2019	Japan	No. of patients= 31 Age (mean) = 69 Gender (Male,%) = 85%	CT	PTX = 100%	OS (median) = 4.4mo, PFS (median) = 2.2mo	PTX monotherapy showed moderate efficacy with acceptable toxicity in heavily treated patients with R/R SCLC patients
Sone *et al.*	2018	Japan	No. of patients = 31 Mean age, years = 72 (>65) Gender (male) = 83.9%	CT = 100%	CT [AMR=100%]	OS (median) = 11.6mo PFS (median) = 5.4mo	AMR has the potential to be an effective regimen for elderly patients with ES-SCLC, in particular for patients with relapsed SCLC
Zhao *et al.*	2019	China	No. of patients= 116 Age ≤65 (180), >65 (92) Gender (Male,%) = 84.9%	CT	TOP/PTX/DTX=100%	OS (median) IRI = 595d; TOP = 154d; PTX = 168.5d; DTX = 184d; PFS (median) IRI = 91d; TOP = 74.5d; PTX = 81d; DTX = 50d	Second-line chemotherapy with TPT in SCLC patients may provide better overall survival benefits

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

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Prophylactic Cranial Irradiation (PCI)							
Stanic *et al.*	2010	Slovenia	No. of patients= 356 Gender (male) = 75% Mean age, years = 61.9 Stage of disease = 48% [LS], 52% [ES]	PCI = 6% CT = 41% CRT = 48.5%	N/A	OS (median) = 21.9mo [PCI] 12.13mo [no PCI] Brain metastases = 25%	Increased median survival time and decreased incidence for brain metastases in patients with PCI. Recommendation to perform PCI in patients with LS disease and good performance status
Nakahara *et al.*	2012	Japan	No. of patients= 17 Mean age, years = 66 [52–78]	PCI = 100%	N/A	Brain metastases (%) = 35% Dementia (incidence) = 29% Gait disturbance (incidence) = 18%	Impact of PCI on neurocognitive functioning is significant and should be weighed against survival benefits, especially in older patients
Ramlov *et al.*	2012	Denmark	No. of patients= 118 Gender (male) = 43% Stage of disease = 62.7% [LS], 37.3% [ES]	PCI = 100% Surgery = 6% CRT = 53% Palliative CT/CRT = 41%	N/A	OS (median) = 24mo [LS], 12mo [ES] Cerebral reoccurrence (%) = 17%	PCI lowers likelihood of developing brain metastases in SCLC
Ozawa *et al.*	2014	Japan	No. of patients= 124 Mean age, years = 65 Stage of disease = 100% [LS]	PCI = 23.3%	N/A	OS (median) = 25.5mo [PCI] 34.5mo [no PCI] Brain metastases (2yrs) = 45.5% [PCI] 29.9% [no PCI]	PCI does not benefit patients with LS-SCLC in conjunction with periodical brain screening and thoracic radiotherapy
Zhu *et al.*	2014	China	No. of patients= 193 Mean age, years = 56 Stage of disease = 100% [LS]	PCI = 34.7% Surgery = 100%	N/A	OS (2y) = 92.5% [PCI] 63.2%, [non-PCI] OS (5yr) = 54.9% [PCI], 47.8% [non-PCI] Brain metastases free survival (2yrs) = 96.8% [PCI], 79.4% [non-PCI]	PCI improves survival and lowers likelihood of developing brain metastases in patients with surgically resected SCLC
Bang *et al.*	2015	Canada	No. of patients= 399 Stage of disease = 100% [ES]	PCI = 17.3% (uptake pre-2008=24.2%; post-2008=57.6%)	N/A	OS (median) = 14mo [PCI], 8.2mo [No PCI] Brain metastases (2yrs) = 40.6% [PCI] 43.8% [No PCI]	PCI in the setting of at least partial response to chemotherapy was found to have a survival benefit and prolongation of time to brain metastasis
Zeng *et al.*	2016	China	No. of patients= 175 Mean age, years = 55 Gender (male) = 73.7% Stage of disease = 88.6% [LS], 11.4% [ES]	PCI = 100%	N/A	OS (5yr) = 48% Brain metastases free survival (2yrs) = 54.9% [PCI]	
Qiu *et al.*	2016	China	No. of patients= 399 Mean age, years = 55 (25–79) Gender (male) = 81% Stage of disease = 100% [LS]	PCI = 46.4% CRT = 100%	N/A	OS (median) = 32.6mo [Early PCI], 40.9 [Late PCI], 21.5 mo [No PCI] Brain metastases (2yrs) = 13% [PCI], 42% [No PCI]	PCI significantly decreased the incidence of brain metastases and improved the overall survival rate in patients with LS-SCLC. Early PCI administered within 6 months of the start of first-line chemotherapy was as effective as late PCI (PCI that was administered 6 months later)

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

Table S2 (*continued*)

Author	Year	Country	Patient characteristics	Treatment received	Regimen	Outcomes	Conclusion
Matutino *et al.*	2017	Brazil	No. of patients= 46 Stage of disease = 100% [ES]	PCI = 35% CT (platinum) = 100%	N/A	OS (median) = 20.94mo [PCI], 11.05 mo [No PCI] PFS (median) = 10.32mo [PCI], 7.66 mo [No PCI] Brain metastases (2yrs) = 19% [PCI], 53% [No PCI]	Careful patient selection for PCI can improve not only brain metastases but also patient survival.
Mamesaya *et al.*	2017	Japan	No. of patients= 79 Mean age, years = 67 (34-83) Gender (male) = 68% Stage of disease = 100% [LS]	PCI = 73.4% [CR =26.5%; PR = 46.8%] CRT = 100%	N/A	OS (median) = Not reached [CR and PCI] 3.2yrs [PR and PCI] Not reached [No PCI] PFS (median) = 7.8yrs [CR and PCI] 1.2yrs [PR and PCI] 1.7yrs [No PCI] Brain metastases (3yrs) = 11.6% [CR and PCI] 34.6% [PR and PCI] 38.1% [No PCI]	PCI may not add clinical benefit to LS-SCLC patients who did not achieve CR after initial therapy if absence of bone metastases could be confirmed by MRI immediately before PCI administration
Soon *et al.*	2018	Singapore	No. of patients= 71 Gender (male) = 83.6% Stage of disease = 100% [ES]	PCI = 22.5% CT = 77.5% [Platinum based = 93%] CRT = 22.5%	N/A	Outcomes presented as univariable and multivariable analyses	Increased utilisation of PCI was observed after publication of the EORTC trial (2006) and PCI was associated with improved survival in patients with at least stable disease following initial chemotherapy
Srivastava *et al.*	2018	New Zealand	No. of patients= 245 Gender (male) = 45% Mean age, years = 63 Stage of disease = 100% [ES]	PCI = 19.5% CT = 89.4% CRT = 11.6%	N/A	OS (median) = 14.3mo [PCI], 6.3mo [No PCI]	Patients who received PCI had improved survival, although this positive association is no longer observed after stratifying patient according to treatment (i.e. chemotherapy and radiotherapy) characteristic
Boskovic *et al.*	2019	Serbia	No. of patients= 200	PCI = 100%	N/A	OS (median) PCI = 19.0m Control = 15.4m	The authors strongly believe that PCI should remain a standard of care for patients with SCLC, after response to initial treatment
Liu *et al.*	2019	China	No. of patients= 385	PCI = 41% CRT = 100%	N/A	OS (median) = 57m; OS (2yrs) = 72.3%; OS (3yrs) = 56.6%; OS (5yrs) = 47.1%	PCI was associated with a significant survival benefit for LS-SCLC patients who had CR to chemoradiotherapy, and prolonged the time to BM, and reduced the cumulative incidence of BM
Cabrero *et al.*	2019	Not available	No. of patients= 98 Stage of disease = 40% [LS] 60% [ES]	PCI = 37.5% RT = 34.7%	N/A	No significant difference in survival between the group treated with RT	We didn't find any difference with PCI or CI in overall survival and BR. A high proportion of the patients in both groups (with/ without BM at diagnosis) didn't receive radiotherapy, due to a very poor clinical status

Table S2 (*continued*)

http://dx.doi.org/10.21037/jtd-20-3034

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Chung *et al.*	2019	Not available	No. of patients= 190 Stage of disease = 100% [ES]	PCI = 27.9%	N/A	OS (1yr) PCI = 45%; No-PCI = 50%; BMFS (1yr) PCI = 86.9%; No-PCI = 52.5%, BMFS (2yr) PCI = 49.8%; No-PCI = 12.7%	Four prognostic factors are associated with a high risk of symptomatic brain metastasis in ED-SCLC: presence of extrathoracic metastases, FDG-PET uptake in BM or spleen, PD after chemotherapy, and high Hb level
Maintenance Chemotherapy							
Yan *et al.*	2018	China	No. of patients = 25	Maintenance CT	Apatanib	OS (median) = 17mo PFS (median) = 8.3mo	Maintenance apatinib was safe and achieved encouraging PFS and OS in extensive-stage SCLC.

AMR=amrubicin, adriamycin, and vincristine, BSC=best supportive care, CAV=cyclophosphamide, adriamycin and vincristine, CE=cisplatin and etoposide, CFRT=conventional fractionation radiotherapy, CR=complete response, CRT=chemoradiotherapy, CCT=concurrent chemotherapy, CCRT=concurrent chemoradiotherapy, CNS=central nervous system, CT=chemotherapy, DFS=disease-free survival, E=etoposide, ES=extensive stage, HFRT=hypofractionated frequency radiotherapy, IRI=irinotecan, IV= intravenous, LDH=lactate dehydrogenase, LS=limited stage, M=extent of external organ involvement (metastases), N=regional lymph node involvement, NSCLC=non-small cell lung cancer, ORR=overall response rate, OS=overall survival, PC=paclitaxel and carboplatin, PCDE=cisplatin, cyclophosphamide, doxorubicin and etoposide, PE=cisplatin and etoposide, PFI=, PS=performance score, PCI=prophylactic cranial irradiation, PEI=cisplatin, etoposide, and ifosfamide, PFS=progression-free survival, RDT=radiotherapy, SCLC=small cell lung cancer, SCRT=sequential chemoradiotherapy, TRT=thoracic radiotherapy, T=characteristics of the primary tumour

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