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Guideline 7-13 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy

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An assessment conducted in December 2019 indicated that Guideline 7-13 REQUIRES UPDATING. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

The systemic treatment recommendations have been superseded by the recommendations in the ASCO guideline. Please refer to the ASCO recommendations.

Guideline 7-13 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/49411

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Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

The objective of this guideline was to make recommendations with respect to thoracic radiotherapy and first-line chemotherapy in the treatment of non-resected patients with small cell lung cancer (SCLC).

As a regular Program in Evidence-Based Care updating process, it was decided to update and combine two guidelines on limited-stage (LS) (stage I, II, and III) SCLC (see Appendix 8) and broaden the scope of the guideline to include extensive-stage (ES) (stage IV) SCLC.

TARGET POPULATION

In keeping with recommendations from the International Association for the Study of Lung Cancer and Cancer Care Ontario, we have transitioned to the use of TNM staging rather than the Veterans Affairs staging of LS versus ES. The target population for this guideline are adult patients with non-resected LS (stage I, II, and III) and ES (stage IV) SCLC who can safely receive definitive radiation.

INTENDED USERS

Clinicians involved in the treatment of non-resected adult patients with LS (stage I, II, and III) and ES (stage IV) SCLC.

RECOMMENDATIONS

The systemic treatment recommendations have been superseded by the recommendations in the ASCO guideline. Please refer to the ASCO recommendations.

Recommendations for Patients with LS (Stage I, II, and III) SCLC

1. Thoracic Radiotherapy

In patients with LS (stage I, II, and III) SCLC, the addition of thoracic radiotherapy to standard chemotherapy is recommended. However, there is no clear evidence to inform definitive recommendations for optimal timing, sequential versus concurrent therapies, and optimal dose or regimen.

a) Optimal Timing

- **Qualifying Statement:**

- It was the consensus of the Working Group members that consultation of radiation oncology should happen as early as possible to facilitate timely therapy with radiation.

b) Sequential or Concurrent

- **Qualifying Statement:**
  - It was the consensus of the Working Group members that concurrent chemotherapy and radiation would generally be considered the standard of care.

c) Dose or Regimen

- **Qualifying Statement:**
  - Currently, dose escalation studies have not shown a benefit in overall survival.
  - The best outcomes in terms of overall survival have been observed in trials using at least 40 Gy in 15 fractions daily or 45Gy in 30 fractions twice daily (or a biologically equivalent dose).

2. Chemotherapy

Etoposide-cisplatin is the preferred regimen for adults who are being treated with combined modality therapy with curative intent.

- **Qualifying Statement:**
  - Although carboplatin is commonly substituted for cisplatin in the etoposide-cisplatin combination, there are insufficient data from clinical trials to demonstrate equivalent outcomes for overall survival.
  - If bolus etoposide-cisplatin is selected as the treatment of choice, there is evidence from one randomized trial that the optimal sequence of administration of the components of the regimen is cisplatin followed by etoposide. The total dose of etoposide per cycle of chemotherapy should be administered in divided doses given daily over three days [1].
  - While not commonly used as a regimen, it is acceptable to offer the alternation of etoposide-cisplatin with cyclophosphamide-doxorubicin-vincristine; however, if this regimen is used, locoregional radiotherapy should not be delivered concurrently with an anthracycline.

a) Typical chemotherapy dosing and schedules used:

Standard chemotherapy doses should be used. The doses and schedules of administration of these recommended chemotherapy regimens are the following:

LS (maximum of 4-6 cycles):

- Cisplatin 75-100 mg/m^2 intravenously (IV) day 1 and etoposide 80-100 mg/m^2 IV days 1-3, every three weeks.
- Cisplatin 25 mg/m^2 IV days 1-3 and etoposide 100 mg/m^2 IV days 1, 2, and 3, every three weeks.
- Carboplatin area under the curve (AUC) 5-6 day 1 and etoposide 100 mg/m^2 IV days 1, 2, and 3, every three weeks.

Recommendations for Patients with ES (Stage IV) SCLC

1. Thoracic Radiotherapy

In patients with ES (stage IV) SCLC, there is insufficient evidence to recommend the addition of thoracic radiotherapy to standard chemotherapy as a standard practice for survival benefit; however, it could be considered on a case-by-case basis to reduce local recurrence.

- **Qualifying Statement:**
  - The following are examples of subgroups of patients that could be considered for thoracic radiotherapy:
    - Low-volume extra-thoracic disease
    - Residual intra-thoracic disease
  - In cases where thoracic radiotherapy is offered to ES SCLC, there is no clear standard for dose or volumes, with dose regimens in trials including 30 Gy in 10 fractions once a day, 45 Gy in 30 fractions twice a day, and 45 Gy in 15 fractions once a day.

There is no evidence to inform definitive recommendations for optimal timing, sequential or concurrent, or dose or regimen.

2. Chemotherapy

In patients with ES SCLC (stage IV), **a** platinum agent plus etoposide is the preferred regimen for adult patients who are being treated with combined modality therapy. Cisplatin and irinotecan represents an alternative treatment option to this, but is associated with increased rates of adverse events such as diarrhea.

- **Qualifying Statement:**
  - A meta-analysis of seven trials of a platinum-etoposide versus a platinum-irinotecan demonstrated modest improvements in overall survival in patients treated with irinotecan. The magnitude of benefit for overall survival was influenced by one trial from Japan and one trial from Korea and it is unclear whether these results may be extrapolated to North American populations. The combination of cisplatin and irinotecan is associated with increased toxicities such as diarrhea, which need to be weighed against modest improvements in overall survival. The clinical importance of this difference is unclear and irinotecan regimens are not currently funded by Cancer Care Ontario for this indication.

a) Typical chemotherapy dosing and schedules used:

Standard chemotherapy doses should be used. The doses and schedules of administration of these recommended chemotherapy regimens are the following:

- Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, and 3, every three weeks.
- Cisplatin 80 mg/m^2 day 1 and etoposide 80 mg/m^2 days 1, 2, and 3, every three weeks.
- Cisplatin 25 mg/m^2 days 1, 2, and 3 and etoposide 100 mg/m^2 days 1, 2, and 3, every three weeks.
- Carboplatin AUC 5-6 day 1 and etoposide 100 mg/m^2 days 1, 2, and 3, every three weeks.

- Cisplatin 60 mg/m^2 day 1 and irinotecan 60 mg/m^2 days 1, 8, and 15, every four weeks.
- Cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 days 1 and 8, every three weeks.
- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m^2 days 1, 8, and 15, every four weeks.

Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

The objective of this guideline was to make recommendations with respect to thoracic radiotherapy and first-line chemotherapy in the treatment of non-resected patients with small cell lung cancer (SCLC).

As a regular Program in Evidence-Based Care (PEBC) updating process, it was decided to update and combine two guidelines on limited-stage (LS) (stage I, II, and III) SCLC (see Appendix 8) and broaden the scope of the guideline to include extensive-stage (ES) (stage IV) SCLC.

TARGET POPULATION

In keeping with recommendations from the International Association for the Study of Lung Cancer and Cancer Care Ontario (CCO), we have transitioned to the use of TNM staging rather than the Veterans Affairs staging of LS versus ES. The target population for this guideline are adult patients with non-resected LS (stage I, II, III) and ES (stage IV) SCLC who can safely receive definitive radiation.

INTENDED USERS

Clinicians involved in the treatment of non-resected adult patients with LS (stage I, II, and III) and ES (stage IV) SCLC.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

The systemic treatment recommendations have been superseded by the recommendations in the ASCO guideline. Please refer to the ASCO recommendations.

Recommendations for Patients with LS (Stage I, II, and III) SCLC

1. Thoracic Radiotherapy

In patients with LS (stage I, II, and III) SCLC, the addition of thoracic radiotherapy to standard chemotherapy is recommended. However, there is no clear evidence to inform definitive recommendations for optimal timing, sequential versus concurrent therapies, and optimal dose or regimen.

a) Optimal Timing

- **Qualifying Statement:**
  - It was the consensus of the Working Group members that consultation of radiation oncology should happen as early as possible to facilitate timely therapy with radiation.
- **Key Evidence:**

- Two randomized controlled trials of aggregate moderate quality reported on overall survival. Overall survival was comparable in both early and late thoracic radiation therapy arms [2,3].
- Two randomized controlled trials of aggregate moderate quality reported on toxicities. A greater percentage of patients in the early thoracic radiation therapy arms experienced non-hematologic toxicities (39% vs. 23%, p=0.001) [2] and greater febrile neutropenia and neutropenia [3] than patients in the late thoracic radiation therapy arms. None of the trials reported on quality of life outcomes.

- **Interpretation of Evidence**

The quality of evidence was considered to be moderate. There was no difference in desirable effects (i.e., with no statistically significant difference in overall survival) and the undesirable effects were moderate (i.e., there was clinically meaningful difference in toxicity). Patients receiving thoracic radiotherapy with the first cycle of chemotherapy showed significantly greater non-hematologic toxicities in one study and grade 3/4 febrile neutropenia and neutropenia in another study. Despite the result of the two trials that showed higher toxicity in the early group, it was the consensus of the Working Group members that the current standard of care was to incorporate thoracic radiation early in the treatment of care. This is reflected in the design of current clinical trials in LS SCLC that utilize radiation upfront with chemotherapy [4-6].

b) Sequential or Concurrent

- **Qualifying Statement:**
  - It was the consensus of the Working Group members that concurrent chemotherapy and radiation would generally be considered the standard of care.

- **Key Evidence:**
  - The current guideline is an update to a previous guideline (Appendix 8). In the previous guideline, a meta-analysis by Pignon et al. [7] examined the question of the timing of thoracic radiotherapy (sequential, alternating, and concurrent) and found no significant differences among the treatment schedules. Pignon et al. [7] was unable to examine toxicity due to heterogeneity. In a randomized controlled trial by Takada et al. [8], patients were randomized to sequential or concurrent thoracic radiotherapy and it was found that median survival times were greater in the concurrent group in comparison to the sequential group (27.2 months vs. 19.7 months). Patients in the concurrent group also showed greater two-year (54.4% vs. 35.1%), three-year (29.8% vs. 20.2%), and five-year (23.7% vs. 18.3%) survival rates when compared with those who received sequential radiotherapy [8]. Patients in the concurrent group had significantly higher rates of leukopenia [8]. In another randomized controlled trial, patients were randomized to chemotherapy combined with concurrent or alternating radiation [9]. The trial was terminated early, but results from the interim analysis indicated that there was no difference in overall survival or mortality related to neutropenia; however, the mortality rate related to pulmonary fibrosis in the concurrent radiotherapy group was higher than in the alternating radiotherapy group.
  - There has been no new evidence to support either concurrent or sequential administration of thoracic radiotherapy reported since the previous guideline.

- **Interpretation of Evidence**
    - While there was no new evidence to support either concurrent or sequential administration of thoracic radiotherapy, it was the consensus of the Working Group members that thoracic radiotherapy should be administered concurrently with chemotherapy based upon current practice, radiobiology and that the very limited data available suggests a trend in improved survival.

c) Dose or Regimen

- **Qualifying Statement:**
    - Currently, dose escalation studies have not shown a benefit in overall survival.
    - The best outcomes in terms of overall survival have been observed in trials using at least 40 Gy in 15 fractions daily or 45 Gy in 30 fractions twice daily (or a biologically equivalent dose).

- **Key Evidence:**
    - Five low- to medium-quality randomized controlled trials reported on overall survival [4,5,10-12]. In all the trials there was no survival advantage of one dose or schedule over another.
    - In terms of toxicity, Faivre-Finn et al. showed that more patients experienced grade 3/4 neutropenia in the hyperfractionated group (45 Gy daily hyperfractioned/30 fractions over 3 weeks) when compared with once daily (66 Gy/33 fractions over 6.5 weeks; 74% vs. 65%, p=0.03); rates of febrile neutropenia were also more elevated, but were non-significant (23.4% vs. 18.0%) [5]. Similarly, in an earlier phase II study by Faivre-Finn et al., the rates of esophagitis were higher in those receiving hyperfractionated thoracic radiotherapy (45 Gy/30 fractions over 15 days) than those in the daily standard (66 Gy/33 fractions over 45 days; 33% vs. 13%) [11]. All other trials reported similar toxicities between groups [4,10,12].
    - Gronberg et al. found that patients in the twice-daily hyperfractioned group had higher rates of dysphagia at the end of thoracic radiotherapy in comparison with those receiving once-daily hypofractionated radiation [12]. There were no other significant differences between groups in global quality of life, dyspnea, or other domains.

- **Interpretation of Evidence:**

The Working Group members believed that overall survival was a critical outcome and toxicity and quality of life were important outcomes for recommendation development. The Working Group members were unanimous in their opinion that patients would value increased survival benefit in addition to acceptable adverse events, although patient input was not sought.

The quality of evidence was considered to be low to moderate. There were no desirable effects (i.e., with no statistically significant difference in overall survival). The best outcomes in terms of overall survival have been observed in trials using at least 40 Gy in 15 fractions once daily or 45 Gy in 30 fractions twice daily [5,13]. The undesirable effects were low (i.e., there was clinically meaningful difference in toxicity). There is some evidence to suggest that patients undergoing hyperfractionated radiation experience greater febrile neutropenia, neutropenia, and esophagitis.

2. Chemotherapy

Etoposide-cisplatin is the preferred regimen for adults who are being treated with combined modality therapy with curative intent.

- **Qualifying Statement:**
  - Although carboplatin is commonly substituted for cisplatin in the etoposide-cisplatin combination, there are insufficient data from clinical trials to demonstrate equivalent outcomes for overall survival.
  - If bolus etoposide-cisplatin is selected as the treatment of choice, there is evidence from one randomized trial that the optimal sequence of administration of the components of the regimen is cisplatin followed by etoposide. The total dose of etoposide per cycle of chemotherapy should be administered in divided doses given daily over three days [1].
  - While not commonly used as a regimen, it is acceptable to offer the alternation of etoposide-cisplatin with cyclophosphamide-doxorubicin-vincristine; however, if this regimen is used, locoregional radiotherapy should not be delivered concurrently with an anthracycline.

- **Key Evidence:**
  - When platinum-etoposide was compared with another platinum agent, non-platinum agent, the addition of another agent to platinum-etoposide, and the addition of a targeted agent to platinum etoposide, trials suggest the combination of cisplatin-etoposide had the greatest overall survival with the least adverse effects.

- **Interpretation of Evidence**

  The quality of evidence was considered to be low to moderate. The differences in desirable effects (i.e., increased survival) were moderate and there were clinically meaningful differences in toxicity. The Working Group members believed that overall survival was a critical outcome and toxicity and quality of life were important outcomes for recommendation development. The Working Group members were unanimous in their opinion that patients would value increased survival benefit in addition to acceptable adverse events, although patient input was not sought.

a) Typical chemotherapy dosing and schedules used:

Standard chemotherapy doses should be used. The doses and schedules of administration of these recommended chemotherapy regimens are the following:

LS (maximum of 4-6 cycles):

- Cisplatin 75-100 mg/m^2 intravenously (IV) day 1 and etoposide 80-100 mg/m^2 IV days 1-3, every three weeks.
- Cisplatin 25 mg/m^2 IV days 1-3 and etoposide 100 mg/m^2 IV days 1, 2, and 3, every three weeks.
- Carboplatin area under the curve (AUC) 5-6 day 1 and etoposide 100 mg/m^2 IV days 1, 2, and 3, every three weeks.

While the data exist for the following combinations, these agents are not routinely used as initial therapy for either LS or ES SCLC:

- Cyclophosphamide 1000 mg/m^2 day 1; doxorubicin (Adriamycin®) 45-50 mg/m^2 IV day 1 and vincristine 1.4 mg/m^2 (maximum dose 2 mg) IV day 1.
- Cyclophosphamide 750-1000 mg/m^2 IV day 1; doxorubicin (Adriamycin) 45-50 mg/m^2 IV day 1; vincristine 1.4 mg/m^2 (maximum dose 2 mg) IV day 1; and etoposide 80-100 mg/m^2 IV days 1-3.
- Cyclophosphamide 1000-1200 mg/m^2 IV day 1; doxorubicin (Adriamycin) 45-50 mg/m^2 IV day 1; and etoposide 50 mg/m^2 IV days 1-3.

  The evidence does not support the routine use of dose-intensive regimens.

- **Key Evidence:**
  - Two trials reported on overall survival and toxicity [14,15]. There was no new evidence to suggest that anything other than the standard chemotherapy doses should be used.

- **Interpretation of Evidence:**

  The Working Group members believed that overall survival was a critical outcome and toxicity and quality of life were important outcomes for recommendation development. They were unanimous in their opinion that patients would value increased survival benefit in addition to acceptable adverse events, although patient input was not sought. The quality of evidence was considered to be low to moderate. The desirable effects (i.e., increased survival) were low and the undesirable effects were low (i.e., there was some clinically meaningful differences in toxicity).

Recommendations for Patients with ES (Stage IV) SCLC

1. Thoracic Radiotherapy

In patients with ES (Stage IV) SCLC, there is insufficient evidence to recommend the addition of thoracic radiotherapy to standard chemotherapy as a standard practice for survival benefit; however, it could be considered on a case-by-case basis to reduce local recurrence.

- **Qualifying Statement:**
  - The following are examples of subgroups of patients that could be considered for thoracic radiotherapy:
    - Low-volume extra-thoracic disease
    - Residual intra-thoracic disease
  - In cases where thoracic radiotherapy is offered to ES SCLC, there is no clear standard for dose or volumes, with dose regimens in trials including 30 Gy in 10 fractions once a day, 45 Gy in 30 fractions twice a day, and 45 Gy in 15 fractions once a day.

- **Key Evidence:**
  - Four randomized controlled trials of aggregate moderate quality reported on overall survival. One study [16] showed improved one-year overall survival with the addition of hyperfractionated radiation to chemotherapy in patients with ES SCLC (65% vs. 46%, p=0.041), while three studies did not show any significant benefit [17-19]. At their primary endpoint, Slotman et al. [19] did not find a significant difference in one-year overall survival; however, in their secondary analysis, a significant improvement in overall survival at 18 months

and two years with the addition of radiation to chemotherapy (18 months: 16% vs. 9%, p=0.03; 2-year overall survival = 13% vs. 3%, p=0.004) was reported. Narayan et al. reported a significant improvement for three years in overall survival; however, there was no significant differences in five-year overall survival [18].

- Slotman et al. reported slightly higher rates of fatigue, insomnia, and headache in the chemotherapy and radiation group; however, these results were not statistically significant [19]. Gore et al. reported similar grade 4 toxicity between both groups [17]. None of the trials reported on quality of life outcomes.

- **Interpretation of Evidence**

Members of the Working Group believed that overall survival was a critical outcome and toxicity and quality of life were important outcomes for recommendation development. Members of the Working Group were unanimous in their opinion that patients would value increased survival benefit in addition to acceptable adverse events, although patient input was not sought.

The quality of evidence was considered to be moderate. The Working Group members believed the desirable effects were moderate (i.e., there was clinically meaningful difference between radiation and chemotherapy versus chemotherapy alone in patients with ES SCLC). However, there was not enough evidence to recommend a change in the standard practice at this time. There were undesirable effects in patients receiving radiation with chemotherapy or chemotherapy; however, the results showed no statistical difference in survival. The Working Group members believed the addition of thoracic radiotherapy to the standard chemotherapy could be considered on a case-by-case basis to reduce the risk of local recurrence. There is good evidence to suggest that the addition of thoracic radiotherapy can reduce local recurrence [17,20]. The consensus of the Working Group was that patients with residual intra-thoracic disease and low-volume extra-thoracic disease may be at greater risk of intra-thoracic progression and that radiotherapy might be considered in these subgroups of patients.

There is no evidence to inform definitive recommendations for optimal timing, sequential or concurrent therapies, or dose or regimen.

2. Chemotherapy

In patients with ES SCLC (stage IV), a platinum agent plus etoposide is the preferred regimen for adult patients who are being treated with combined modality therapy. Cisplatin-irinotecan represents an alternative treatment option to this, but is associated with increased rates of adverse events such as diarrhea.

- **Qualifying Statement:**
  - A meta-analysis of seven trials of a platinum plus etoposide versus a platinum plus irinotecan demonstrates modest improvements in overall survival in platinum plus irinotecan. The magnitude of benefit for overall survival was influenced by one trial from Japan and one trial from Korea and it is unclear whether these results may be extrapolated to North American populations. The combination of cisplatin and irinotecan is associated with increased toxicities such as diarrhea, which need to be weighed against modest improvements in overall survival. The clinical importance of this difference is

unclear and irinotecan regimens are not currently funded by CCO for this indication.

- **Key Evidence:**
  - For patients with ES SCLC, seven trials of moderate aggregate quality were included in the meta-analyses that compared overall survival for platinum-irinotecan and platinum-etoposide (See Systematic Review). Patients who received irinotecan had a longer overall survival compared with those who received etoposide (hazard ratio [HR], 0.84; 95% confidence interval [CI], 0.74 to 0.95; p=0.006). There was, however, evidence of statistical heterogeneity (I^2=52%, X^2=12.48, p=0.05). A sensitivity analysis was conducted with the Noda et al. trial [21] removed because there was an a priori suspicion that the Japanese population may respond differently to irinotecan. With this trial removed, the results still demonstrated a significant benefit for irinotecan (HR, 0.88; 95% CI, 0.79 to 0.98; p=0.02; I^2=31%, X^2=7.24 [degrees of freedom (df)=5]; p=0.20). In an exploratory analysis excluding Asian trials [21,22], the HR was 0.87 (95% CI, 0.76 to 1.00; p=0.05, I^2=45%, X^2=7.23 [df=4], p=0.12).
  - Three randomized control trials [23-25] of moderate aggregate quality were included in a meta-analysis that compared overall survival for platinum-topotecan and platinum-etoposide (See Systematic Review). Patients who received topotecan did not have longer overall survival compared with those who received etoposide (HR, 0.97; 95% CI, 0.87 to 1.07; p=0.55).
  - Eight randomized controlled trials compared platinum-irinotecan versus platinum-etoposide for toxicity for patients with ES SCLC [21,22,26-31]. In patients receiving irinotecan-platinum, there were significantly fewer reported cases of neutropenia [21,26], anemia [26,29], thrombocytopenia [21,26,27,29,30], and febrile neutropenia [26], and significantly more reported cases of diarrhea [22,27-29]. A large study conducted by Kim et al. found that there were significantly more frequent cases of grade 3/4 anemia and nausea in the irinotecan-platinum group [22].
  - Three randomized controlled trials compared topotecan/cisplatin with cisplatin-etoposide [23-25]. In one trial, patients received oral topotecan with IV cisplatin and found that patients had higher rates of leukopenia, thrombocytopenia, and anemia in the oral topotecan group [23]. In two large studies where patients received topotecan-cisplatin, there were significantly fewer cases of neutropenia [24], anemia [24], and leukopenia [25]. In one trial, there were more cases of thrombocytopenia [24], and fewer in the other trial [25].

- **Interpretation of Evidence**

The Working Group members believed that overall survival was a critical outcome and toxicity and quality of life were important outcomes for recommendation development. The Working Group members were unanimous in their opinion that patients would value increased survival benefit in addition to acceptable adverse events, although patient input was not sought.

The quality of evidence was considered to be low to moderate. The differences in desirable effects (i.e., increased survival) were large with moderate undesirable effects. Evidence from the meta-analysis on platinum-irinotecan and evidence from trials that compared platinum-etoposide with another platinum agent, a non-platinum agent, the addition of another platinum agent, or the addition of a targeted agent showed a large

desirable effect. There is some evidence to suggest difference between North American and Japanese populations, which may limit generalizability [21,28].

a) Typical chemotherapy dosing and schedules used:

Standard chemotherapy doses should be used. The doses and schedules of administration of these recommended chemotherapy regimens are the following:

- Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, and 3, every three weeks.
- Cisplatin 80 mg/m^2 day 1 and etoposide 80 mg/m^2 days 1, 2, and 3, every three weeks.
- Cisplatin 25 mg/m^2 days 1, 2, and 3 and etoposide 100 mg/m^2 days 1, 2, and 3, every three weeks.
- Carboplatin AUC 5-6 day 1 and etoposide 100 mg/m^2 days 1, 2, and 3, every three weeks.
- Cisplatin 60 mg/m^2 day 1 and irinotecan 60 mg/m^2 days 1, 8, and 15, every four weeks.
- Cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 days 1 and 8, every three weeks.
- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m^2 days 1, 8, and 15, every four weeks.

While data exist for the following combinations, these agents are not routinely used as initial therapy:

- Cyclophosphamide 1000 mg/m^2 day 1; doxorubicin (Adriamycin) 45-50 mg/m^2 IV day 1; and vincristine 1.4 mg/m^2 (maximum dose 2 mg) IV day 1.
- Cyclophosphamide 750-1000 mg/m^2 IV day 1; doxorubicin (Adriamycin) 45-50 mg/m^2 IV day 1; vincristine 1.4 mg/m^2 (maximum dose 2 mg) IV day 1; and etoposide 80-100 mg/m^2 IV days 1-3.
- Cyclophosphamide 1000-1200 mg/m^2 IV day 1; doxorubicin (Adriamycin) 45-50 mg/m^2 IV day 1; and etoposide 50 mg/m^2 IV days 1-3.

The evidence does not support the routine use of dose-intensive regimens.

- **Key Evidence:**
  - One trial evaluated optimal doses for overall survival and toxicity [32]. In this trial, patients were randomized to conventional cisplatin-etoposide or dose-intensified therapy with cisplatin-etoposide. There were no significant differences between groups for overall survival. Patients receiving the conventional cisplatin-etoposide experienced significantly greater neutropenia and less thrombocytopenia in comparison to the dose-intensified group
  - Nine trials reported on overall survival. These looked at varying schedules and regimens [33-41]. Trials of cisplatin-etoposide regimens comparing sequential and alternating schedules found a similar median overall survival between groups [33,34]. There was a trend in increased overall survival in favour of six-cycle therapy in comparison to four-cycle therapy [40]. Masutani et al. compared dose-intensive weekly alternating and standard alternating cycles of cyclophosphamide, doxorubicin, and vincristine, finding that the weekly regimen showed significant improvements in survival time [35].
  - In a phase II trial of daily versus continuous infusion schedules of topotecan, it was found that the median survival of the daily infusion was higher (18 months vs. 12.5 months, p=nr) [36]. The continuous infusion schedule was closed early

due to insufficient activity [36]. In another phase II study comparing cisplatin-etoposide plus irinotecan administered weekly or every four weeks, it was found that the median survival in patients in the weekly schedule was higher (12.9 months vs. 8.9 months, p=nr) [38]. Interestingly, a study comparing cisplatin-irinotecan followed by cisplatin-etoposide and the reverse sequence found overall survival to be similar in both groups [41].

- Seven trials reported on toxicity [33-38,41]. The percentage of patients experiencing neutropenia was significantly higher in the daily schedule versus continuous [36], in those receiving chemotherapy every four weeks versus weekly schedule [38], and if receiving cisplatin-etoposide followed by cisplatin-irinotecan [41]. Patients in the daily schedule also experienced higher levels of leukopenia [36]. The remaining trials showed similar toxicity between the schedule comparisons.

- **Interpretation of Evidence**

The Working Group members believed that overall survival was a critical outcome and toxicity and quality of life were important outcomes for recommendation development. The Working Group members were unanimous in their opinion that patients would value increased survival benefit in addition to acceptable adverse events, although patient input was not sought.

The quality of evidence was considered to be low to moderate. The desirable effects (i.e., increased survival) were low and the undesirable effects were low (i.e., there was some clinically meaningful differences in toxicity).

IMPLEMENTATION CONSIDERATIONS

The Working Group members considered the recommendations around platinum-etoposide to reflect standard of care and is easily implementable. The evidence would support platinum-irinotecan as an alternative treatment to platinum-etoposide. Differences in toxicity exist that might influence a physician's choice of therapy. However, irinotecan is currently not approved by Health Canada for the treatment of SCLC. Therefore, it would be challenging to implement any recommendations around the use of irinotecan in SCLC.

The Working Group members believe the outcomes valued by clinicians will align with the outcomes valued by patients and most patients and healthcare providers will view the recommendations as acceptable. The Working Group members also believe that these recommendations will not require additional training for the providers.

RELATED GUIDELINES

- Kotalik J, Yu E, Markman BR, Evans WK; Members of the Lung Cancer Disease Site Group. Prophylactic cranial irradiation in small cell lung cancer. Yu E, Souter L, reviewers. Toronto (ON): Cancer Care Ontario; 2003 Nov [EDUCATION AND INFORMATION 2013]. Program in Evidence-based Care Practice Guideline Report No.: 7-13-2. EDUCATION AND INFORMATION 2013
- Members of the Lung Cancer Disease Site Group. Chemotherapy for relapsed small cell lung cancer. Toronto (ON): Cancer Care Ontario; 2006 Aug [Endorsed 2012 Dec 11]. Program in Evidence-based Care Evidence-based Series No.: 7-17 Version 2

Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The PEBC is an initiative of the Ontario provincial cancer system, CCO. The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

As a regular updating process, it was decided to update and combine two guidelines on LS SCLC (stage I, II, III; see Appendix 8) and broaden the scope of the guideline to include ES SCLC (stage IV).

GUIDELINE DEVELOPERS

This guideline was developed by the Lung Cancer Disease Site Group (DSG; Appendix 1), which was convened at the request of the Disease Pathway Management Group. The project was led by a small Working Group, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology, radiation oncology, and health research methodology. Other members of the Lung Cancer DSG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [42,43]. This process includes a systematic review, interpretation of the evidence and draft recommendations by the Working Group, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [44] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to search for existing systematic reviews and primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts. For this project, the following databases were searched for existing guidelines that addressed the research questions: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase. Websites of the following guideline developers were also searched: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia. MEDLINE and EMBASE were search for guidelines for the period of 1996 to June 2016 (Appendix 3). Guidelines were considered potentially relevant if they were based on a systematic review and relevant to the guidelines objectives and research questions. Only English evidence-based guidelines less than five years old were considered. This search for existing guidelines yielded nine guidelines [45-53]. None of these guidelines were considered suitable for endorsement or adaptation as a source document for the full project. A search of the primary literature was required (see Section 4 Evidence Review).

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

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- Max Chen and Ananya Nair for conducting a data audit.
- Sara Miller for copy editing.

Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy

Section 4: Systematic Review

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in Canada, with an estimated 26,580 new cases and 20,900 deaths from lung cancer in 2015 [54]. Approximately 10% to 15% of patients with lung cancer have SCLC, the most aggressive of all types of lung cancer [54]. SCLC is divided into two stages: limited disease stage (stage I, II, and III) and extensive disease stage (stage IV). LS SCLC is local or regional, where the cancer is only on one side of the chest (one lung and possibly the lymph nodes on the same side of that lung). In ES SCLC, the cancer has spread more widely in the lung, to the other lung, to lymph nodes on the other side of the chest, or even to other parts of the body. At presentation, approximately 70% to 75% of patients will have ES SCLC, whereas the remaining 25% to 30% will have LS SCLC [54]. The median survival for patients with LS SCLC undergoing standard therapy is 16 to 24 months and for patients with ES SCLC it is six to 12 months.

Chemotherapy is the most common treatment for SCLC due to its aggressive nature and early metastatic spread. Platinum-based chemotherapy is the standard of care for first-line therapy for LS SCLC and ES SCLC. The most commonly used platinum agents are cisplatin and carboplatin, which are often combined with the non-platinum agent etoposide. The use of chemotherapy and thoracic radiation therapy reflects the current standard of care for patients with LS SCLC [55,56]. The addition of thoracic radiation therapy to standard combination chemotherapy improves both local control and overall survival [55]. Two previous guidelines have examined the role of thoracic radiation therapy as an adjunct to standard chemotherapy [55] and the role of combination chemotherapy in the initial management of LS SCLC [57]. This review will update this evidence as well as broaden the scope to include ES SCLC. This review does not address the prophylactic cranial irradiation in SCLC, which is covered in Guideline 7-13-2.

The Working Group developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. For non-resected patients with ES SCLC, what are the benefits and harms in terms of overall survival, quality of life, and toxicity for chemotherapy and thoracic radiotherapy versus chemotherapy alone?
2. For non-resected patients with LS SCLC or ES SCLC undergoing chemotherapy, what are the benefits and harms in terms of overall survival, quality of life, and toxicity for early versus late thoracic radiotherapy?
3. For non-resected patients with LS SCLC or ES SCLC undergoing chemotherapy, what are the benefits and harms in terms of overall survival, quality of life, and toxicity for sequential versus concurrent thoracic radiotherapy?
4. For non-resected patients with LS SCLC or ES SCLC, what is the optimal dose and schedule of radiation with respect to overall survival, quality of life, and toxicity?
5. For non-resected patients with LS SCLC or ES SCLC, are there differences in the relative benefits and harms of chemotherapy combinations studied?

6. For non-resected patients with LS SCLC or ES SCLC, what is the optimal dose and schedule of chemotherapy with respect to overall survival, quality of life, and toxicity?

METHODS

As a regular updating process, it was decided to update and combine two guidelines on LS SCLC (see Appendix 8) and broaden the scope of the guideline to include ES SCLC. The evidence review of the guideline is based on three different searches over time: (1) the original search from the guideline on the role of thoracic radiation therapy in LS SCLC conducted from 1996 to 2002 [55], (2) the original search from the guideline on the role of combination chemotherapy in LS SCLC conducted from 1996 to 2002 [57], and (3) the new search to update the evidence on LS SCLC from 2002 to the present date and to include evidence on ES SCLC from 1996 to the present date for this new version of the guideline. Only the methods for this new search are described in detail here. The methods from the originals guidelines were described elsewhere and can be found in Appendix 8.

A literature search strategy (see Appendix 2 for search strategy) was developed and conducted using the Cochrane Library, MEDLINE, and EMBASE databases for the period 1996 to June 2016. The search included guidelines, systematic reviews, and randomized controlled trials. Systematic reviews were evaluated based on their clinical content and relevance prior to screening the primary studies. Systematic reviews published as components of practice guidelines (not otherwise considered suitable for adaptation or endorsement) were also considered. The intent was to determine whether there were reviews that could form the literature base for this guideline instead of conducting a new systematic review. Any identified systematic reviews that addressed the research questions were assessed using a Measurement Tool to Assessment Systematic Reviews (AMSTAR) [58]. The results of the AMSTAR assessment were used to determine whether any existing review could be incorporated as part of the evidentiary base. Abstracts from conferences of the ASCO, American Society for Radiation Oncology, and World Lung Cancer Conference were searched for years 1996-June 2016 using EMBASE and MEDLINE, and the conference websites.

Study Selection Criteria and Process

A review of the titles and abstracts and subsequent full-text review (if warranted) was conducted by one reviewer (LDDA).

Inclusion Criteria:

- Studies included full reports or abstracts of meta-analyses or randomized controlled trials with more than 30 participants comparing chemotherapy plus thoracic radiotherapy with chemotherapy alone, early with late thoracic radiotherapy, sequential with concurrent thoracic radiotherapy, different doses of thoracic radiotherapy, combination chemotherapeutic regimens, duration of chemotherapy, or schedules of chemotherapy for the first-time treatment of patients with LS SCLC or ES SCLC.
- Studies that reported data on overall survival, quality of life, or toxicity.

Exclusion Criteria:

- Data for patients with LS SCLC were not reported separately from data for patients with ES SCLC and vice versa.
- Trials that used chemotherapy regimens containing procarbazine and/or lomustine or another nitrosourea (e.g., cyclophosphamide-methotrexate-vincristine-lomustine chemotherapy) were not considered. The use of regimens containing these agents has largely been abandoned in North America because of the adverse

effects associated with them and because of the availability of other regimens of equal efficacy and reduced toxicity.
- Studies of palliative treatment were excluded.
- Trials of granulocyte-colony stimulating factor where the dose or administration schedules of the chemotherapy are the same on both the experimental and control arms.
- Trials that did not use an appropriate contemporary standard of care as a control arm.
- Papers published in a language other than English

Data Extraction and Assessment of Study Quality and Potential for Bias

Ratios, including HRs, were expressed with a ratio <1.0 indicating benefit of the investigational treatment compared with the control. All extracted data and information were audited by an independent auditor.

Important quality and completeness of reporting features for randomized trials, such as sample size calculations, number of patients, statistical significance of outcomes, Cochrane Risk of Bias Tool, and whether analysis was on a intent-to-treat basis were extracted for each study. Studies in which effectiveness of randomization is suspect due to unequal group characteristics have a notation added. Blinding of outcome assessment was rare and therefore not used as criteria for assessment. Extraction of data on toxicity was generally limited to significant differences between treatment arms in severe (grade 3+) adverse events.

The GRADE method for assessing the quality of aggregate evidence was used for each comparison using the GRADEpro Guideline Development Tool [59]. The outcomes were rated for their importance for decision making by the Working Group members. Only those outcomes that were considered critical or important were included in the GRADE evidence tables. Five factors were assessed for each outcome in each comparison. These included the risk of bias, inconsistency, indirectness, imprecision, and publication bias. The Kaplan-Meier curves from each of the studies were visually inspected for overall survival at 12 months and the median was calculated [60].

Synthesizing the Evidence

When clinically homogeneous results from two or more trials were available, a meta-analysis was conducted using the Review Manager software (RevMan 5.3 provided by the Cochrane Collaboration) [61]. For time-to-event outcomes, the HR, rather than the number of events at a specific time, is the preferred statistic for meta-analysis, and is used as reported. If the HR and/or its standard error were not reported, they have been derived from other information reported in the study, using the methods described by Parmar et al. [62] The generic inverse variance model with random effects was used. Statistical heterogeneity was calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic was less than or equal to 10% ($p \leq 0.10$) and/or I^2 greater than 50% was considered indicative of statistical heterogeneity.

RESULTS

The original literature search from the Cochrane Library, MEDLINE, and EMBASE, after removal of duplicates, resulted in 5142 citations. Preliminary sorting resulted in 3626 randomized controlled trials, 563 systematic reviews or meta-analyses, and 953 guidelines.

Search for Existing Systematic Reviews

Of the 563 systematic reviews or meta-analyses found in the literature search, 51 remained after application of inclusion/exclusion criteria. The results of the AMSTAR assessment were used to determine whether any existing review could be incorporated as part of the evidentiary base (Appendix 3). The AMSTAR assessments indicated important deficiencies in quality in many of the systematic reviews. No systematic reviews were found that addressed our research questions and adhered to our study eligibility criteria. They were therefore only used as a source of references. A full review of the primary randomized controlled trials was required.

Search for Primary Literature

Literature Search Results

A total of 3626 English and foreign-language studies were identified. Two hundred ninety-six were selected for full-text review. Of those, 64 met the pre-defined eligibility criteria for this systematic review [2-5,10-12,14-19,21-41,63-92]. The search flow diagram is available in Appendix 4.

Study Design and Quality

Fifty-five fully published reports [2-4,10,12,14-16,19,21,23,24,26-41,63,64,66,67,69-91] and nine abstracts [5,11,17,18,22,25,65,68,92] were found. The characteristics and outcomes of the included studies and GRADE quality of evidence of included studies can be found in Tables 4-1 to 4-20, the methodological quality assessment of the studies can be found in Appendix 5, and the Cochrane risk of bias judgments for included studies in Appendix 6. Approximately one-third of the fully published papers gave details of the randomization process suggesting allocation concealment. There was no indication that allocation was not concealed or that researchers influenced the treatment received. In the majority of trials, the baseline characteristics were well balanced with respect to patient and disease characteristics, with the exception of the following trials: >5% weight loss [63], slightly older patients in one group [27], median body mass index [78], and more brain and lung metastases [34,91]. While not routinely reported, most trials appeared to be of open design without blinding of investigators or participants. The power and required sample size were calculated and reported in the majority of studies, but were not calculated in four trials [39-41,91]. Fifteen trials were partially terminated early (i.e., one arm in the study) or fully terminated early due to slow accrual [10,14,15,25,32,36], unacceptable toxicity [24,73,74,87], interim analysis showed benefit to one group over another/no meaningful difference between groups [21,39], negative effects in another trial [68], or due to futility after planned interim analysis [17,88].

In conducting the GRADE quality assessment, in many cases it was impossible to create a summary of the outcome of interest due to the heterogeneity in the way the outcome was reported and heterogeneity in doses and schedules of radiation and/or chemotherapy. Therefore, in the GRADE evidence profiles in this review no summary estimate column is provided; the reader should refer to the preceding outcome table for the outcomes by trial or the accompanying meta-analysis for that topic. Also, conference abstracts were considered to be at serious risk of bias according to the GRADE framework, as the reporting is often incomplete and may change between abstract and full publication, or may never be fully reported.

Outcomes

1. ***For non-resected patients with ES SCLC, what are the benefits and harms in terms of overall survival, quality of life, and toxicity for chemotherapy and thoracic radiotherapy versus chemotherapy alone?***

The characteristics and outcomes of the included studies comparing chemotherapy and thoracic radiotherapy versus chemotherapy alone can be found in Table 4-1. Two full-text publications [16,19] and two abstracts were found [17,18]. The quality of the aggregate evidence for the outcomes the Working Group believed to be critical and important can be found in Table 4-2. The quality of the evidence was low to moderate and was downgraded due to risk of bias, inconsistency in the trials, and imprecision.

Four moderate aggregate quality randomized controlled trials reported on overall survival. One study [16] showed an improved one-year overall survival with the addition of hyperfractionated radiation to chemotherapy in patients with ES SCLC, while three studies did not [17-19]. Slotman et al. reported that for the primary endpoint of one-year overall survival that the addition of thoracic radiotherapy to standard chemotherapy did not improve overall survival, but secondary analysis did find significant improvements in 18-month and two-year overall survival [19]. Similarly, Narayan et al. reported a significant improvement for three-year overall survival; however, five-year overall survival was non-significant [18].

Three low aggregate quality randomized controlled trials reported on adverse effects. One study showed significantly more grade 4 nausea/vomiting and alopecia for patients undergoing chemotherapy alone compared with chemotherapy and thoracic radiotherapy [16]. While not significant, patients also showed greater leukopenia, thrombocytopenia, and anemia. Slotman et al. reported slightly higher rates of fatigue, insomnia, and headache in the chemotherapy and radiation group; however, these results were not statistically significant [19]. Gore et al. reported similar grade 4 toxicity in both groups [17].

None of the trials reported on the quality of life outcome.

Table 4-1. Studies selected for inclusion for ES SCLC comparing chemotherapy with chemotherapy and thoracic RT.

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number of pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusion
Jeremic et al. 1999 [16] Phase NR Yugoslavia, Jan 1988- June 1993	206 pts aged 18-70 years old with no prior treatment or previous malignancy (except skin non-melanoma) underwent 3 wks PE (80 mg/m² D1;80 mg/m² D1-3). All pts underwent PCI. If CR/CR or PR/CR, randomized	Group 1: ACC HFX RT (54 Gy/36 fx) + CE (50 mg each on each RT day) followed by PCI and 2 cycles of PE	55	Group 1 vs. 2: Mean Survival Time: 17 mths vs. 11 mths, p=nr 1 yr OS: 65% vs. 46%, p=0.041 5 yr OS: 9.1% vs. 3.7%, p=nr	Grade 4 (%): Group 1 vs. 2 Leukopenia: 13 vs. 20, p=0.18 Thrombocytopenia: 11 vs. 14, p=0.23 Anemia: 5 vs. 11, p=0.39 Infection: 9 vs. 9, p=0.64 Nausea/vomiting: 5 vs. 14, p=0.0038 Alopecia: 4 vs. 22, p<0.001	NR	Addition of ACC HFX RT led to improved OS in a subset of pts than chemo alone.
		Group 2: 2 cycles of PE, followed by PCI, and 2 cycles of PE	54				
Narayan et al. 2015 [18] *Abstract* Phase III India July 2008 - Dec 2009	358 pts undergoing PE (60-80 mg/m² D1; 80-120mg/m² D1-D3) x 3 cycles for 3 wks. All patients underwent PCI If CR/CR or PR/CR, randomized	Group 1: ACC HFX RT (45 Gy/1.5 twice daily) + PE ×4	144	Group 1 vs. 2: 1 yr OS: 39% vs. 31%, p=nr HR = 0.89 (95% CI 0.69-1.13), p=0.091 3 yr OS: 18% vs. 11%, p=nr HR = 0.83 (95% CI 0.72-1.08), p=0.047) 5 yr OS: 10.3% vs. 6.2%, p=nr HR = 0.83 (95% CI 0.49-1.29, p=0.47)	NR	NR	Chemo RT may be used as a continuum treatment in pts after induction chemo.
		Group 2: PE x4 alone without RT	143				
Slotman et al. 2015 [19] Phase III Netherlands, UK, Norway, Belgium Feb 2009 - Dec 2012	498 pts ≥18 yrs and WHO PS 0-2 underwent 4-6 cycles of standard chemo (PE; no dose provided). Within 6 wks or less were randomized. All pts underwent PCI	Group 1: PE + RT (30 Gy in 10 fx)	247	Group 1 vs. 2 1 yr OS: 33% (95% CI 27-39) vs. 28% (95% CI 22-34), p=nr HR = 0.84 (0.69-1.01), p=0.066 Median OS 8 mths 18 mths OS: 16% vs. 9%, p=0.03 2 yr OS: 13% (9-19) vs. 3% (2-8), p=0.004	Grade 3 (%): Group 1 vs. 2 Cough: 0.0 vs. 0.4 Dysphagia: 0.4 vs. 0.0 Dyspnea 1.2 vs. 1.6 Esophagitis: 1.6 vs. 0 Fatigue: 4.5 vs. 3.2 Insomnia: 1.2 vs. 0.8 Nausea/vomiting: 0.4% vs. 0 Headache: 1.2 vs. 0.8	NR	Addition of RT after any response to chemo suggests significant OS at 2 years.
		Group 2: PE (no RT)	248				
Gore et al. 2015 [17] RTOG 0937 Phase II Unknown Mar 2010 - Feb 2015	86 pts underwent 4-6 cycles of platinum-based chemo (no dose/drug provided). Stratified according to PR vs. CR after chemo, 1 vs. 2-4 metastatic lesions, age<65 vs. >65 years. All pts underwent PCI (25 Gy/10fx)	Group 1: RT (30 Gy in 10 fx or-45 Gy in 15 fx)	44	OS 1 yr: 50.8% (95% CI 34.0-65.3%)	Grade 4 toxicity- 1 pt Grade 5 respiratory failure -1 pt	NR	Observed OS exceeded predicted OS for both arms. Consolidative RT did not improve 1 yr OS
		Group 2: No RT	42	OS 1yr: 60.1% (95% CI 41.2 - 74.7%)	Grade 4 toxicity- 1 pt		

Abbreviations: ACC = accelerated; CAV/EP = cyclophosphamide, doxorubicin, vincristine/etoposide cisplatin; CE = carboplatin/etoposide; chemo = chemotherapy; CODE = cisplatin, vincristine, doxorubicin, etoposide; CR/CR = complete response local and distant levels; D = day; ES = extensive-stage; fx = fraction; HFX = hyperfractionated; HR = hazard ratio; mths = months; NR = not reported; OS = overall survival; PCI = prophylactic cranial irradiation; PE = etoposide/cisplatin; PR/CR = partial response within thorax and complete response elsewhere; pt(s) = patient(s); RT = radiation therapy; SCLC = small cell lung cancer; WHO PS = World Health Organization performance status; yr = year

Table 4-2. Quality of evidence for studies selected for inclusion for ES SCLC comparing chemotherapy with chemotherapy and thoracic radiotherapy.

Quality assessment							Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Overall Survival								
4	RCT	serious [1]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	CRITICAL
Toxicity								
3	RCT	not serious	serious [2]	not serious	serious [3]	none	⊕⊕◯◯ LOW	IMPORTANT

Abbreviations: ES = extensive-stage; RCT = randomized controlled trial; SCLC = small cell lung cancer
GRADE Working Group grades of evidence
High quality = We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality = Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality = We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

1. Primary endpoint for Slotman et al. study was 1 overall survival [19], which turned out to be negative. At 2 OS, there was a significant difference.
2. Inconsistency between trials, one showing chemotherapy + radiation therapy was more toxic while the other is reverse. Not large % difference however.
3. Number of events is lower

2. For non-resected patients with LS SCLC and ES SCLC undergoing chemotherapy, what are the benefits and harms in terms of overall survival, quality of life, and toxicity for early versus late thoracic radiotherapy?

The characteristics and outcomes of the included studies comparing early versus late thoracic radiotherapy are presented in Table 4-3. Two full-text publications reported data on patients with LS SCLC [2,3] and no evidence was found for patients with ES SCLC. The quality of the aggregate evidence for overall survival and toxicity can be found in Table 4-4. The quality of the evidence was moderate and was marked down for imprecision, as the CIs of one trial on overall survival were wide and also because of the number of events is lower for toxicity scores.

In terms of overall survival, the aggregate quality of the randomized controlled trial was moderate. Overall survival was comparable in both early and late thoracic radiotherapy arms. Spiro et al. showed improvement in one-year, two-year, and three-year overall survival for patients receiving late thoracic radiotherapy, but the HRs between the groups was non-significant [2]. Sun et al. revealed a slightly higher median overall survival for the early thoracic radiotherapy; however, the two-year overall survival showed a greater percentage of patients surviving in the late thoracic radiotherapy group [3]. The five-year overall survival for both groups was similar.

The aggregate quality of the randomized controlled trials reporting on toxicity was moderate. Sun et al. [3] found that patients undergoing early thoracic radiotherapy experienced greater hematologic toxicities such as febrile neutropenia, neutropenia, and anemia. Similarly, Spiro et al. [2] found that non-hematologic toxicities were significantly greater in those undergoing early thoracic radiotherapy, while hematologic toxicities were similar.

None of the trials reported on quality of life outcomes.

3. For non-resected patients with LS SCLC and ES SCLC undergoing chemotherapy, what are the benefits and harms in terms of overall survival, quality of life, and toxicity for sequential versus concurrent thoracic radiotherapy?

The literature review found no trials meeting our inclusion criteria comparing sequential versus concurrent thoracic radiotherapy for non-resected patients with LS SCLC and ES SCLC undergoing chemotherapy.

Table 4-3. Studies selected for inclusion for LS SCLC* patients undergoing chemotherapy comparing early TRT and late TRT.

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Arms or comparisons	OS	Toxicity	Quality of Life	Authors' Conclusion
Spiro et al. 2006 [2] Phase NR United Kingdom 1993-1999	325 pts age <75 years, ECOG PS 0-3 and no previous chemo or RT undergoing CAV (1000 mg/m^2; 50 mg/m^2; 2 mg/m^2) on day 1 of a 3-week cycle, alternating with PE (25 mg/m^2; 100 mg/m^2) administered on days 1 to 3, for a total of 6 cycles.	Early Group: TRT of 40 Gy in 15 fx over 3 weeks, delivered concurrently with the first cycle of PE (week 3) Late Group: TRT of 40 Gy in 15 fx over 3 weeks, delivered concurrently with the sixth cycle of chemo (i.e., third cycle of PE; week 15).	159 166	Early vs. Late: Median OS: 13.7 mths vs. 15.1 mths, p=nr 1 yr: 56% vs. 61% p=nr 2 yr: 22% vs. 31% p=nr 3 yr: 16% vs. 22% p=nr Unadjusted (Kaplan-Meier curve) HR 1.16 (95% CI 0.91-1.47, p=0.23 Adjusted HR = 1.23 (95% CI 0.96-1.58), p=nr	Nonhematologic toxicities (early vs. late) 39% vs. 23%, p=0.001 Hematologic toxicities (31% vs. 30%, p=0.89)	NR	No evidence of a difference in survival between patients who received early or late TRT
Sun et al. 2013 [3] Phase III South Korea July 2003-June 2010	220 pts with ECOG PS ≤2 and no previous chemo or RT undergoing PE (70 mg/m^2 D1; 100 mg/m^2 D1-3) every 3 weeks for 4 cycles.	Early Group: TRT (52.5 Gy with 2.1 Gy/fx, once a day, 5x a week for 5 consecutive weeks) to begin on day 1 of first cycle of PE Late Group: TRT (52.5 Gy with 2.1 Gy/fx, once a day, 5x a week for 5 consecutive weeks) to begin on day 1 of third cycle of PE	111 108	Early vs. Late: Median OS 26.8 mths (22-32) vs. 24.1 mths (20-28),p=nr 2 yr OS: 50.7% vs. 56.0%, p=nr 5 yr OS: 24.3% vs. 24.0%, p=nr	Grade 3 or 4 Hematologic toxicities (early vs. late): Febrile neutropenia: 21.6% vs. 10.2% Neutropenia: 70.3% vs. 59.3% Anemia: 9.9% vs. 6.5%	NR	OS comparable in both early and late TRT arms. Late TRT administered with the third cycle of PE seemed to not be inferior to early TRT.

Abbreviations: CAV = cyclophosphamide, doxorubicin, vincristine; CI = confidence interval; D = day; ECOG PS = Eastern Cooperative Oncology Group performance status; ES = extensive stage; fx = fractions; HR = hazard ratio; LS = limited stage; OS = overall survival; mths = months; PE = cisplatin/etoposide; SCLC = small cell lung cancer; RT = radiotherapy; TRT = thoracic radiotherapy

*No studies on ES SCLC were found

Table 4-4. Quality of evidence for studies selected for inclusion for LS SCLC comparing early versus late TRT.

Quality assessment							Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Overall survival								
2	RCT	not serious	not serious	not serious	serious	none	⊕⊕⊕◯ MODERATE	CRITICAL
Toxicity								
2	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations: LS = limited-stage; RCT = randomized controlled trial; SCLC = small cell lung cancer; TRT = thoracic radiotherapy

1. Number of events is lower

4. For non-resected patients with LS SCLC or ES SCLC, what is the optimal dose and schedule of radiation with respect to overall survival, quality of life, and toxicity?

The characteristics and outcomes of the included studies comparing the optimal dose and schedule of thoracic radiotherapy are presented in Table 4-5. Three full publications [4,10,12] and two abstracts [5,11] reported data on patients with LS SCLC. No trials were found for patients with ES SCLC. Aggregate scores of the trials were not possible as each trial had different doses and/or schedules. Therefore, the quality of the individual trial evidence for overall survival, toxicity, and quality of life can be found in Table 4-6.

Five trials reported outcome data for overall survival [4,5,10-12] and ranged from low to medium quality. In all trials there was no significant survival advantage of one dose or schedule over another. The majority of trials were small, and not powered to answer questions about overall survival. The largest trial compared 45 Gy daily hyperfractionated radiation (30 fractions over 3 weeks) with the daily dose of 66 Gy (33 fractions over 6.5 weeks); there was no significant difference between the two groups [5]. Schild et al. showed no improvement in overall survival in 45 Gy split-course hyperfractionated radiation when compared with the daily standard of 50.4 Gy [4]. Studies conducted by Blackstock et al. and Faivre-Finn et al. also found no significant difference in median overall survival, showing that split-dose radiation is tolerable in patients but does not provide a survival advantage [10,11]. Lastly, the study by Gronberg et al. compared twice-daily hyperfractionated thoracic radiotherapy (40 Gy/30 fractions) with once-daily hypofractionated (42 Gy/15 fractions) and found no statistically significant difference in overall survival [12].

Five trials reported outcome data for toxicity [4,5,10-12]. Faivre-Finn et al. showed that significantly more patients experienced grade 3/4 neutropenia in the hyperfractionated group (45 Gy daily hyperfractioned) [5]. Rates of febrile neutropenia were also more elevated in patients in the hyperfractionated group, but this was non-significant [5]. Similarly, an earlier phase II study by Faivre-Finn et al. found that rates of esophagitis were higher in those receiving hyperfractionated thoracic radiotherapy (45 Gy daily) [11]. All other trials reported similar toxicity between groups [4,10,12].

There was one randomized controlled trial that reported on quality of life [12]. Gronberg et al. found that patients in the twice-daily hyperfractioned group had higher rates of dysphagia at the end of thoracic radiotherapy in comparison to those receiving once-daily hypofractionated RT. There were no other significant differences between groups in global quality of life, dyspnea, or other domains.

Table 4-5. Studies selected for inclusion for LS-SCLC patients undergoing chemotherapy comparing optimal dose and schedule of TRT.

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
Blackstock et al. 2005 [10] Phase III US Aug 1987 - Nov 1992	110 pts with no previous treatment, >18 years old with an ECOG PS 0-3 were randomized. All underwent chemo cycles (3 wks) of PE (60 mg/m^2 D1; 120 mg/m^2 D1-3;) for cycles 1,2,5 and CAV (750 mg/m^2/60 mg/m^2/2.0 mg D1) for cycles 3,4,6.	Arm A: 50Gy daily standard fx (25 fx, 2.0Gy/day, 5 days/wk concomitantly D1 with first 2 cycles of PE)	56	Arm A vs. B Median: 14.0 mths vs. 15 mths, p=nr 2 yr OS: 36% vs. 31%, p=nr 5 yr OS: 18% vs. 17%, p=nr	Grade 3/4, A vs. B Anemia: 5% vs. 2% Thrombocytopenia: 7% vs. 9% Neutropenia: 64% vs. 67% p=nr	NR	Split-dose RT was tolerable in pts but did not provide a survival advantage.
		Arm B: 50Gy split course ("interdigitated") hypofractionated (20 fx, 2.5Gy/day, D8-17 during first 2 21-day cycles of chemo and D8 and D11 during 3rd 21-day cycle)	54				
Schild et al. 2004 [4] Phase III North America Sept 1990-Nov 1996	324 pts with ECOG PS ≤ 2 received 6 cycles of PE (30 mg/m^2; 130 mg/m^2 cycles 1-3, 100mg/m^2 cycles 4-6) 3 days duration, separated by 28 days 261 pts randomized on 3rd cycle	Arm A: 50.4Gy daily standard fx (28 fx weekdays, total 38 days) PE continued during RT cycles 4-5	131	Arm A vs. B Median survival: 20.6 mths vs. 20.6 mths 2 yr OS: 44.3% vs. 44%, p=ns 5 yr OS: 22.1% vs. 22%, p=ns	Arm A vs. B, Grade 4+ Hematologic 44% vs. 42%, p=0.84 Nonhematologic 9% vs. 14% p=0.24	NR	Unable to detect an advantage for twice daily vs. once daily
		Arm B: 48 Gy split course hyperfractionated (32fx, weekdays, at least 4 hrs apart). After initial 24 Gy, RT was held for 2.5 wks and resumed 28 days (5th cycle of PE)	130				
Faivre-Finn et al. 2011 [11] *abstract* Phase II Mar 2008	38 pts with PS 0-1 received PE (60 mg/m^2 D1; 120mg/m^2 D1-3), ever 3 wks x4 cycles with concurrent RT from cycle 2	OD: 66 Gy daily standard in 33 fx	12	OD vs. BID Median OS = 16.9 mths vs. 15.5 mths, p=0.926 1-yr OS: 65% vs. 67%	OD vs. BID: Grade 3 esophagitis: 13% vs. 33% Grade 3 pneumonitis 4% vs. 0% Grade 3 dsypnea at 6-9 mths: 4% vs. 11%	NR	No statistical significant differences in OS and both groups had acceptable rates of late RT-related toxicity
		BID: 45Gy daily BID/hyper fractionated in 30 fx	26				

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
Gronberg et al. 2016 [12] Phase II Norway May 2005-Jan 2011	171 pts undergoing 4 course of PE (75mg/m^2 D1/100mg/m^2 D 1-3) every 3 weeks Age ≥18 years, WHO PS 0-2, no prior chest radiotherapy	Arm A: 45 Gy/30 fx (twice-daily hyperfractionated) in blocks of 8, received between 3-4 wks after 1st course PE D1	73	BID vs. OD Median = 25.1 mths (95% CI 16.9 - 33.3) vs. 18.8 mths (95% CI 13.6-23.9), p=0.61 1 yr OS: 77% (95% CI 67-87) vs. 76% (95% CI 67-85), p=0.94 2 yr OS 53% (95% CI 42-65) vs. 42% (95% CI 31-52), p=0.14) 4 yr OS 25% (95% CI 15-35) vs. 25% (95% CI 16-34), p=0.96	Grade 3-4 (BID vs. OD) Neutropenic infections 37% vs. 44%, p=0.37 Esophagitis : 33% vs. 31%, p=0.80 Pneumonitis: 3% vs. 2%, p=1.0	HRQoL: dysphagia at end of RT: OD 61, BID, 72, p=nr, but difference in mean of 10 pts is clinically relevant. No other differences in global QoL, dysphagia, dyspnea, or other domain	No statistical significant differences in OS, though median OS was higher in twice daily TRT arm.
		Arm B: 42 Gy/15 fx (once daily hypofractionated) in blocks of 8, received between 3-4 wks after 1st course PE D1	84				
Faivre-Finn et al. 2016 [5] *abstract* Apr 2008-Nov 2013	547 patients undergoing 4 to 6 cycles of PE (25 mg/m^2 d 1-3 or 75 mg/m^2 D1 with E 100 mg/m^2 days 1-3), followed by PCI if indicated	66 Gy daily standard fx (33fx over 6.5 wks)	273	A vs. B: 2 OS: 51% (45-57) vs. 56% (50-61), p=nr Median OS= 25 mths (21-31) vs. 30 mths (24-34), p=nr HR 1.17 (0.95-1.45), p=0.15	A vs. B Grade 3/4 neutropenia 65% vs. 74%, p=0.03 Febrile neutropenia 18% vs. 23.4%, p=nr esophagitis 19% vs. 19%, p=nr radiation pneumonitis 2.5% vs. 2.2%, p=nr	NR	OD RT did not result in superior survival or worse toxicity than BID RT, supporting the use of either regimen for standard of care treatment
		45 Gy daily BID/hyperfractionated (30 fx over 3 wks)	274				

Abbreviations: BID = twice-daily radiation; CAV = cyclophosphamide, doxorubicin, vincristine; D = day; ECOG = Eastern Cooperative Oncology Group; fx = fraction; HRQoL = health-related quality of life; mths = months; OD = once-daily radiation; OS = overall survival; PCI = prophylactic cranial irradiation; PE = cisplatin/etoposide; PS = performance status; RT= radiotherapy; TRT = thoracic radiotherapy; WHO = World Health Organization; wks = weeks; yr = year

Table 4-6. Quality of evidence for studies selected for inclusion for LS SCLC comparing optimal dose and schedule of thoracic radiotherapy.

Quality assessment								Quality	Importance
Study	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
LS: Overall Survival									
Blackstock 2005 [10]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Schild 2004 [4]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Faivre-Finn 2011 [11]	1	RCT	serious [2]	not serious	not serious	serious [1]	none	⊕⊕◯◯ LOW	CRITICAL
Gronberg 2015 [12]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Faivre-Finn 2016 [5]	1	RCT	serious [2]	not serious	not serious	serious [3]	none	⊕⊕◯◯ LOW	CRITICAL
LS: Toxicity									
Blackstock 2005 [10]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Schild 2004 [4]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Faivre-Finn 2011 [11]	1	RCT	serious [2]	not serious	not serious	serious [1]	none	⊕⊕◯◯ LOW	IMPORTANT
Gronberg 2015 [12]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Faivre-Finn 2016 [5]	1	RCT	serious [2]	not serious	not serious	serious [1]	none	⊕⊕◯◯ LOW	IMPORTANT
LS: Overall Survival									
Gronberg 2015 [12]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations: LS = limited-stage; RCT = randomized controlled trial; SCLC = small cell lung cancer

1. Number of events is lower and only one study
2. Conference Abstract

5. For non-resected patients with LS SCLC or ES SCLC, are there differences in the relative benefits and harms of chemotherapy combinations studied?

Platinum-other versus Platinum-Etoposide

The characteristics and outcomes of the included studies comparing the platinum-etoposide combination versus other platinum combinations are presented in Table 4-7. Two full publications reported data on patients with LS SCLC [63,69], and 13 full publications [21,23,24,26-31,63,69,88,90] and two abstracts [22,25] reported data on patients with ES SCLC.

a) LS SCLC

Aggregate scores of the trials were not possible as the experimental arms of the two trials reported on different types of chemotherapy [63,69]. The quality of the individual trial evidence for overall survival, toxicity, and quality of life can be found in Table 4-8.

Two moderate-quality trials reported on overall survival and toxicity [63,69]. In Artal-Cortes et al., patients received either cisplatin-epirubicin or cisplatin-etoposide; the median overall survivals were comparable, however with a significant elevated rate of neutropenia was seen in the cisplatin-etoposide group [63]. Kubota et al. compared cisplatin-irinotecan versus cisplatin-etoposide and found that patients in the cisplatin-etoposide group had a slightly higher median three-year, and five-year overall survival; however, these results were not statistically significant [69]. Patients receiving cisplatin-etoposide had higher rates of leukopenia and neutropenia.

b) ES SCLC

In total, eight trials compared platinum-irinotecan versus platinum-etoposide for overall survival for patients with ES SCLC [21,22,26-31]. Data for overall survival from seven trials of moderate aggregate quality were included in the meta-analyses (Table 4-9). Shi et al. was excluded from this analysis as it is a phase II trial and does not provide the necessary information for a meta-analysis [30]. Two trials did not specifically report HR [26,28] and the methods described in Parmar et al. [62] were used to calculate an estimated HR. In addition, the inverse of HR was used in two cases [27,29] to reflect that a value <1 favours the experimental group.

Patients who received irinotecan had longer overall survival compared with those who received etoposide (HR, 0.84; 95% CI, 0.74 to 0.95; p=0.006; Figure 4-1). There was, however, evidence of statistical heterogeneity (I^2=52%, X^2=12.48, p=0.05). A sensitivity analysis was conducted with the Noda et al. trial removed because there was an a priori suspicion that pharmacogenomics differences in the Japanese population may result in different outcomes with irinotecan [21]. With this trial removed, the results still demonstrated a significant benefit for irinotecan, while eliminating statistical heterogeneity (HR, 0.88; 95% CI, 0.79 to 0.98; p=0.02; I^2=31%, X^2=7.24 [df=5]; p=0.20). In an exploratory analysis excluding Asian trials [21,22], the HR was 0.87 (95% CI, 0.76 to 1.00; p=0.05, I^2=45%, X^2 =7.23 [df=4], p=0.12).

The overall survival at 12 months was estimated by visual inspection of each of the Kaplan-Meier curves from the trials and the median of the overall survivals at 12 months was 38%; therefore, the baseline risk of mortality was estimated to be 62%. At a 62% risk of mortality, there would be 6.4% (64 per 1000) fewer deaths at 12 months (95% CI from 19 fewer to 109 fewer) for patients in the platinum-irinotecan arm.

Table 4-7. Studies selected for inclusion for LS SCLC and ES SCLC comparing platinum-other vs. platinum-etoposide

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
LS							
Artal-Cortes et al. 2004 [63] Phase III, 15 hospitals Spain Jun 1994 to Mar 1998	411 pts between the ages of 18-75 with life expectancy of >12 wks, Karnofsky perfomance index ≥60% were randomized to a chemo treatment group, and then treated with TRT 50 Gy	Arm A: Cisplatin (100 mg/m^2 D1) + epirubicin (100 mg/m^2 D1) every 3 wks for 6 cycles Arm B: PE (100 mg/m^2 D1; 100 mg/m^2 D 1-3) every 3 wks for 6 cycles	100 107	A vs. B: 12.9 mths (11.7-14.6) vs. 12.9 mths (11.4-14.5), p=0.3	Grade 4, A vs. B Hemoglobin 8.0% vs. 4.2%, p=ns Neutophils 34.0% vs. 40.0%, p=0.005 Platelets 12.0% vs. 9.5%, p=0.29	NR	Cisplatin/epirubicin is similar to PE, with lower toxicity and fewer treatment visits
Kubota et al. 2014 [69] Phase 3, 36 institutions Japan Sept 2002-Oct 2006	281 patients with previously untreated LS received PE (80mg/m^2 D1; 100 mg/m^2 D1-3) + AHTRT (1.5 Gy twice daily, 5 days/wk, total 45 Gy over 3 weeks). Pts w/out progression were randomized. Age 20-70 years, ECOG PS 0-1, adequate organ function	IP (60 mg/m^2 D1, 8, 15; 60 mg/m^2 D1), treated every 3-4 weeks for 3 cycles PE (80 mg/m^2 D1; 100 mg/m^2 D1-3) repeated every 3 weeks for 3 cycles	129 129	IP vs. PE: median OS 2.8 (2.4-3.6) vs. 3.2 yrs (2.4-4.1) 3 yr OS: 46.6% (37.7-55.1) vs. 52.9% (43.9-61.1) 5 yr OS 33.7 (25.5-42.0) vs. 35.8% (27.4-44.1; HR 1.09 (0.80-1.46), log test p=0.70	IP vs. PE: Leukopenia 19% vs. 27% Anemia 6% vs. 9% Thrombocytopenia 0 vs. 3% Neutropenia 30% vs. 68% Vomiting 4% vs. 2% Febrile neutropenia 14% vs. 16% p=nr for all	NR	This study indicates that 4 cycles of PE + concurrent AHTRT should continue to be the standard of care.
ES: Irinotecan							
Hanna et al. 2006 [26] Phase 3 Australia, US, and Canada Dec 2000 through Jun 2003	331 pts with measurable disease, adequate hematologic, hepatic, and renal function, ECOG PS of 0-2 and no prior anticancer systemic therapy were randomly assigned	IP (65 mg/m^2 D1&8; 30 mg/m^2 D1&8) every 21 days, min 4 cycles PE (60 mg/m^2 D1; 120 mg/m^2 D1-3), every 21 days, min 4 cycles	221 110	IP vs. PE: Median: 9.3 mths (0.1-32.6) vs. 10.2 mths (0.3-44.6), p=0.74 1 yr OS: 34.95% vs. 35.19% 2 yr OS 8.0% vs. 7.9%	Grade 3-4 (IP vs. PE): Neutropenia 36.2 % vs. 86.5%, p<0.01 Anemia 4.8% vs. 11.5%, p=0.03 Thrombocytopenia: 4.3% vs. 19.2%, p<0.01 Febrile neutropenia: 3.7% vs. 10.4%, p=0.06	NR	IP can be an equally effective regimen with a different toxicity profile that can be used when it is anticipated that hematologic toxicity will be limiting or when found to be severe during early cycles of PE

Hermes 2008 et al. [27] Phase III Norway Dec 2001- Jul 2005	220 pts were randomly assigned age >18 yrs and adequate hematologic, hepatic, and renal function. No upper age limit or limit for WHO PS	IC: irinotecan (175 mg/m^2) D1 IV + carboplatin (AUC = 5) every 21 days for 4 cycles	105	IC vs. CE Median: 8.5mths vs. 7.1 mths, p=0.02 CE relative to IC HR 1.41 (1.06-1.87), p 0.02	IC vs. CE (%) Leukopenia 33 vs. 34, p=nr Anemia 5 vs. 8, p=nr Thrombocytopenia 15 vs. 26, p=0.05 Diarrhea 11 vs. 1, p=0.003	EORTC QLQ-C30- no dif. on global QoL, functioning, symptom scales at baseline or f/u	Induction chemo with IC prolongs OS compared with oral EC without compromising QoL.
		CE (AUC =5 D1) + 120 mg/m^2 D1-5) every 21 days for 4 cycles	104				
Kim et al. 2013 [22] *abstract* Korea multi center, dates unknown	362 pts were randomized until disease progression or until unacceptable toxicity	IP: cisplatin (70 mg/m^2 IV D1) + irinotecan (65 mg/m^2 IV D1&8), every 3 weeks for max 6 cycles	173	IP vs. PE Median: 10.9 mths vs. 10.3 mths HR = 0.879 (0-1.054), p=0.1207	Grade 3/4 anemia, nausea and diarrhea more frequent in IP (no values reported) No dif. for neutopenia, thrombocytopenia, neutopenic fever, infection	NR	IP failed to show superiority in OS compared with EP in Korean pts.
		PE (70 mg/m^2 IV D1; 100 mg/m^2 IV D1-3), every 3 weeks for max 6 cycles	189				
Lara 2009 [28] Phase III North America Nov 2002-Mar 2007	651 pts with no prior RT, chemo or surgery, Zubrod PS of 0-1, life expectancy of at least 3 mths were randomly assigned	IP (60 mg/m^2 D1,8,15; 60 mg/m^2 D1), 4 wk cycle	324	IP vs. PE: Median OS 9.9 mths (9.2-11.1 mths) vs. 9.1 mths (8.4-9.9 mths), p=0.71 Estimated 1 yr survival rates: 41% vs. 34%	IP vs. PE Grade 3-4 (Neutopenia -33% vs. 68% Thrombocytopenia 4% vs. 15% Diarrhea 19% vs. 3% Infection 11% vs. 18% Cardiovascular 10% vs. 12% Renal 4% vs. 4% Hepatic 3% vs. 5%	NR	EP remains the reference treatment standard in North America.
		PE (80 mg/m^2 D1; 100 mg/m^2 D1-3), 3 wk cycle	327				
Noda et al. 2002 [21] Phase II Japan Nov 1995-Nov 1998	Patients with no prior chemo, RT, or surgery, measurable lesions, ECOG PS of 0-2, age < 70 yrs, life expectancy > 3 mths, and adequate hematologic, hepatic, and renal function were randomized	IP (60 mg/m^2 D1,8,15; 60 mg/m^2 D1), four 4 wk cycles	77	IP vs. PE Median: 12.8 mths (11.7-15.2) vs. 9.4 (8.1-10.8), p=0.002 HR = 0.60 (0.43-0.83), p=nr 1 OS 58.4% (47.4 - 69.4) vs. 37.7% (26.8 - 48.5) 2 OS: 19.5% (10.6 vs. 28.3) vs. 5.2%(0.2-10.2)	Grade 3-4 (%), IP vs. PE Neutropenia 65.3 vs. 92.2, p<0.001 Leukopenia 26.7 vs. 51.9, p=0.002 Anemia 26.7 vs. 29.9, p=0.72 Thrombocytopenia 5.3 vs. 18.2, p=0.02	NR	IP is an attractive option for pts with good PS.
		PE (80 mg/m^2 D1; 100 mg/m^2 D1, 2, 3), four 3wk cycles	77				

Schmittel et al. 2011 [29] Phase III Germany, 8 institutions Aug 2002- Sept 2008	216 pts with no prior chemo, life expectancy >3 mths, Karnofsky PS >50% were randomized	IC: Irinotecan (50 mg/m^2 D1, 8, 15) + carboplatin (AUC 5 D1), repeated on day 29	106	IC vs. CE Median: 10.0 mths (8.4-11.6) vs. 9.0 (7.6-10.4), p=0.06 HR (CE vs. IC)=1.34 (0.97-1.85), p=0.06	Grade 3-4 (%), IC vs. CE Anemia 17 vs. 28, p=0.029 Leukopenia 24 vs. 60, p<0.001 Thrombocytopenia 23 vs. 46, p<0.001 Diarrhea 14 vs. 5, p=0.018	NR	PE or CE should remain standard treatment
		CE (AUC5=D1; 140 mg/m^2 D1-3), repeated on day 22	110				
Shi et al. 2015 [30] Phase II China Apr 2010-Dec 2012	62 patients with ECOG PS 0-2, life expectancy of at least 3 month, aged between 18-70 yrs were randomized	Irinotecan (65 mg/m^2 D1 & 8) + cisplatin (75 mg/m^2 D1), 3 weeks	30	IP vs. PE Median 18.1 mths vs. 15.8 mths, p=nr	Grade 3-4 (%), IP vs. PE Neutropenia 53.3 vs. 71.9, p=0.057 Leukopenia 43.3 vs. 53.1, p=0.291 Anemia 30.0 vs. 31.3, p=0.114 Thrombocytopenia 6.7 vs. 18.8, p=0.035	NR	Failed to show a significant superiority in efficacy in the IP regimen compared with PE
		PE (75 mg/m^2 D1; 100 mg/m^2 D1-3), 3 weeks	32				
Zatloukal et al. 2010 [31] Phase III 59 centers across 12 countries Sept 2003-June 2007	407 pts with WHO 0-1, age 18-75. adequate hematology clinical biochemistry and organ function, and no previous RT or surgery on the primary tumour were randomized	IP: Irinotecan (65 mg/m^2 D1 & 8) + Cisplatin (80 mg/m^2 D1), 3 weeks for up to 6 cycles	202	IP vs. PE Median 10.2 (9.0-11.7) vs. 9.7 (8.9-11.1) HR = 0.81 (0.65-1.01), p=0.06 1 OS 41.9% vs. 38.9% 2 OS 16.3% vs. 8.2%	IP vs. PE Anemia 6.9 vs. 6.4 Neutropenia 38.1 vs. 59.6 Thrombocytopenia 5.4 vs. 4.4 Leukopenia 6.4 vs. 9.9	NR	Study failed to show significant superiority in OS in IP treatment compared with standard. However, IP can be considered equally effective as the EP regimen with different toxicity profile
		PE (80 mg/m^2 D1; 100 mg/m^2 D1, 2, 3), 3 weeks for up to 6 cycles	203				

ES: Topotecan							
Eckardt et al. 2006 [23] Phase 3 31 countries July 2001 to Apr 2003	784 pts from 176 centres in 31 countries who were ≥18 yrs old, had no prior chemo, and ECOG PS ≤2 were randomly assigned	Oral topotecan 1.7 mg/m^2/d D1-5 with IV cisplatin 60 mg/m^2 /d on D5. Administered as 21 day cycles for 4 cycles or 2 cycles beyond best response. PE (IV etoposide 100 mg/m^2/d D1-D3 with cisplatin 80 mg/m^2/d on D1. Administered as 21 day cycles for 4 cycles or 2 cycles beyond best response.	389 395	A vs. B: Median: 39.3 wks (37.4-42.4) vs. 40.3 wks (37.1-43.6) 1 yr OS: 31% (27-36%) vs. 31% (27-36%) HR = 1.05 (0.904-1.236), p ns	Grade 4 Leukopenia 12% vs. 7% Neutropenia 26% vs. 58% Thrombocytopenia 9% vs. 6% Anemia 8% vs. 6% p=nr for all	AUC: topotecan/cisplatin was 58.68 and 60.55 for PE, absolute difference of 1.87 points, p=0.049	While oral topotecan provided similar efficacy and tolerability, it was not superior to PE
Fink et al. 2012 [24] Phase 3 Germany; Austria Aug 2002- Feb 2006	795 pts aged 18-75, adequate bone marrow, hepatic, and renal function and ECOG PS < 2 were randomized into 3 groups. The 3rd group (topotecan/etoposide; n = 91) was prematurely discontinued after unacceptable toxicity	TP: Topotecan (1 mg/m^2) from D1 through 5, cisplatin 75 mg/m^2 on day 5, every 3 weeks, 6 cycles PE (75 mg/m^2 D1; 100 mg/m^2 D1-3), every 3 weeks, 6 cycles	346 334	TP vs. PE: Median (CI): 44.9 wks (41.4- 48.1) vs. 40.9 wks (36.7- 46.1) HR (95% CI) TP vs. PE = 0.92 (0.78-1.08), p=0.30 1 yr Survival rate: 32.6 wks (27.6-37.7) vs. 36.7 wks (31.6-41.8) OR =1.20 (95% CI 0.873- 1.649), p=0.23	PE vs. TP (%) Grade 4 Neutropenia: 27.2 vs. 37.7 p=0.004 Sepsis: 1.7 vs. 1.2, p=nr Grade 4 Thrombocytopenia: 6.9 vs. 2.4, p=0.006 Grade 4 Anemia: 3.5 vs. 0.9, p=0.034	NR	Combination of IV TP is an active regimen and is non-inferior to the standard PE. TP was associated with higher percentage of hematological toxicities and treatment related deaths.
Mau-Soerensen 2014 [25] Phase III abstract Denmark	281 patients were randomly assigned	Topotecan (2.0 mg/m^2 IV D1-3) + cisplatin (50 mg/m^2 IV D3), 6 cycles CE (AUC = 5 IV D1; 120 mg/m^2 , D1-3), 6 cycles	~140 ~141[1]	TP vs. CE Median OS 10.9 mths vs. 9.8 mths 2 yr OS: 9.2% vs. 8.7% HR= 0.87 (0.67-1.17), p=0.26	TP vs. CE (%) Leukopenia 6.7 vs. 21.1, p<0.01 Thrombocytopenia 5.2 vs. 12.8, p<0.01	NR	No difference in OS comparing TP and CE
ES: Other							
Artal-Cortes et al. 2004 [63] Phase III, 15 hospitals Spain Jun 1994 to Mar 1998	411 pts were randomized to a chemo treatment group. Age 19-75 yrs, life expectancy of >12 wks, Karnofsky perfomance index ≥60%	Cisplatin (100 mg/m^2 D1) + Epirubicin (100 mg/m^2 D1) every 3 wks for 6 cycles PE (100 mg/m^2 D1; 100 mg/m^2 D 1-3) every 3 wks for 6 cycles	100 95	A vs. B: 8.1 (6.8-9.5) vs. 7.9 (7.0-9.0), p=0.22	Grade 4 Hemoglobin 3.0% vs. 6.5%, p=0.39 Neutropenia 59.8% vs. 48.0%, p=0.007 Platelets: 7.0% vs. 5.6%, p=0.18	NR	Cisplatin/epirubicin similar to PE, with lower toxicity and fewer treatment visits

Oh et al. 2016 [78] Phase III Korea, 14 centers Jan 2009-Jan 2013	147 pts from 14 centres aged between 19-80 yrs, no previous chemo or RT, ECOG PS ≤2 and a life expectancy of ≥12 weeks.	BP: Belotecan (0.5 mg/m^2 mixed with 100 mL 5% dextrose D1-4) + cisplatin (60 mg/m^2 D1), 3 wk cycle	71	BP vs. PE: Median: 360 days (285-482) vs. 305 (232-343), p=0.210	BP vs. PE (%) Febrile neutropenia 15.7 vs. 7.8, p=0.196 Anemia 34.3 vs. 13.0, p=0.003 Leukopenia 60.0 vs. 45.5, p=0.098 Neutropenia 77.1 vs. 67.5, p=0.204 Thrombocytopenia 54.3 vs. 16.9, p<0.001	NR	BP regimen is non-inferior to the EP regimen
		PE (60 mg/m^2 D1; 100mg/m^2 D1-3), 3 wk cycle	76				
Socinski et al. 2009 [88] Phase III Aug 2006-Dec 2007 25 institutions in 25 countries	908 pts with ECOG PS 0-2, no prior chemo, immuno, or biologic therapy and ≥18 yrs were randomly assigned	Permetrexed (500 mg/m^2 D1) + carboplatin(AUC=5 D1), repeated every 3 wks for a max of 6 cycles	433	Permetrexed vs. CE Median: 8.1 mths vs. 10.6 mths HR = 1.56 (1.27-1.92), p<0.01 1 OS 26% (20-32) vs. 40% (33-48)	Permetrexed vs. CE (%) Neutropenia: 11 vs. 47, p<0.001 Anemia: 11 vs. 7.4, p=0.049 thombocytopenia: 9.5 vs. 10, p=0.735 Leukopenia: 4.2 vs. 8.3, p=0.012 Febrile neutropenia 1.4 vs. 4.5, p=0.009	NR	Permetrexed-carboplatin was inferior to CE
		CE (AUC=5 D1; 100 mg/m^2 D1, 2, 3), repeated every 3 wks for a max of 6 cycles	447				
Sun et al. 2016 [90] Phase III China Jun 2008- Jul 2010	300 pts with ECOG PS 0-1, ≥18 yrs, adequate hematological, hepatic function, and minimum life expectancy of ≥3 mths, were randomly assigned	AP: Amrubicin (40 mg/m^2 , D 1-3) + cisplatin (60 mg/m^2 D1), once every 21 days for 4-6 cycles	149	AP vs. PE: Median 11.8 (11.0-12.6) vs. 10.3 mths (9.2-12.0) HR 0.81 (0.63-1.03), p=0.08 1 OS 48.6% (CI 40.3-56.4) vs. 41.9% (CI 34.0-49.7)	AP vs. PE, Grade 3-4 (%) Anemia 6.7 vs. 6.7 Leukopenia 34.9 vs. 19.3 Neutropenia 54.4 vs. 44.0 Thrombocytopenia 16.1 vs. 7.3 p=nr for all	NR	AP was non inferior to EP therapy, suggesting AP has sufficient efficacy; however, EP is still gold standard
		PE (Chinese standard of cisplatin 80 mg/m^2 D1; 100 mg/m^2 D1-3), once every 21 days for 4-6 cycles	150				

Abbreviations: AH TRT = accelerated hyperfractionated thoracic radiotherapy; AP = amrubicin/cisplatin; AUC = area under the curve; BP = belotecan/cisplatin; CE = carboplatin/etoposide; CI = confidence interval; D = day; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; EORTC-QLQ = European Organization for Research and Treatment of Cancer Quality of Life questionnaire; f/u = follow up; HR = hazard ratio; IC = irinotecan/carboplatin; IP = irinotecan/cisplatin; NR = not reported; OS = overall survival; PE = cisplatin/etoposide; PS = performance Status; QoL = quality of life; RT = radiotherapy; TC = topotecan/carboplatin; TP = topotecan/cisplatin; TRT = thoracic radiotherapy; WHO = World Health Organization; wks = weeks; yrs = years

1 Exact number per group were not specified

Table 4-8. Quality of evidence for LS SCLC comparing platinum-etoposide vs. platinum-other

Quality assessment								Quality	Importance
Platinum-Other regimen	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
LS: Overall Survival									
Epirubicin + P	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
IP	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
LS: Toxicity									
Epirubicin + P	1	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
IP	1	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations: LS = limited-stage; IP = irinotecan/cisplatin; P = cisplatin; RCT = randomized controlled trial; SCLC = small cell lung cancer

1. Only one study
2. Number of events is lower and only one study

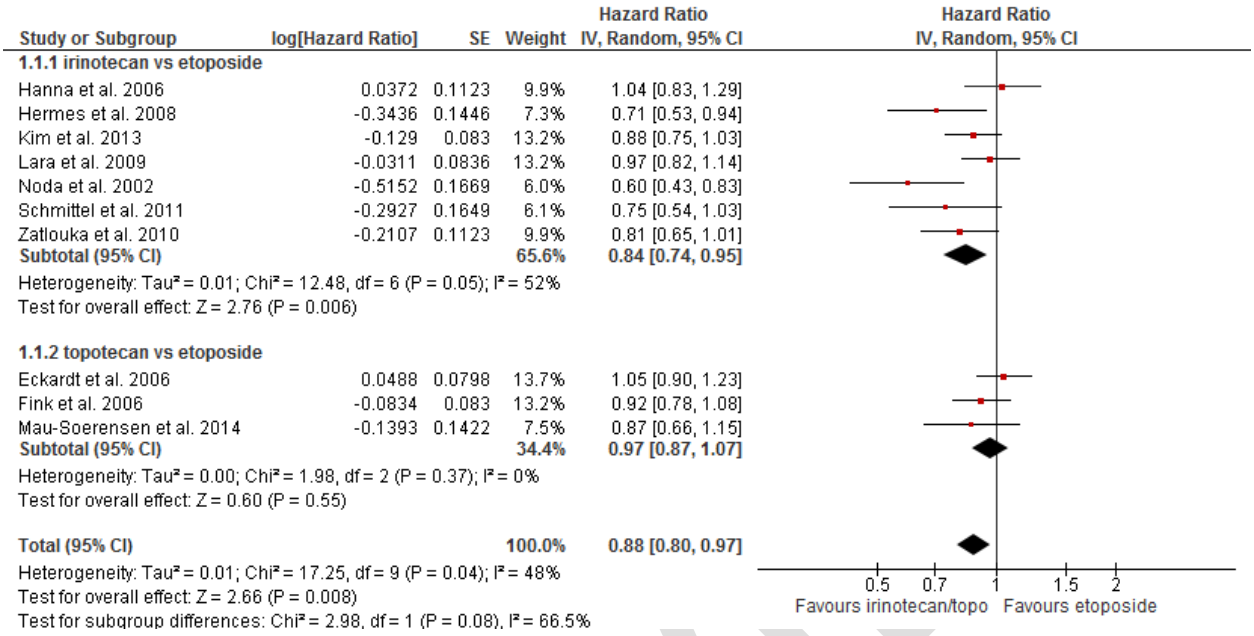
Table 4-9. Quality of evidence for ES SCLC comparing platinum-etoposide vs. platinum-other

Quality assessment								№ of patients		Effect		Quality	Importance
Platinum other	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum Etoposide	Platinum other	Relative (95% CI)	Absolute (95% CI)		
Overall Survival													
Irinotecan	7	RCT	not serious	not serious	not serious	not serious	none	1121	1211 Baseline risk 62.0%	HR 0.84 (0.74 to 0.95)	64 fewer per 1,000 (from 19 fewer to 109 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Topotecan	3	RCT	not serious	not serious	not serious	not serious	none	425	450 Baseline risk 64.0%	HR 0.97 (0.87 to 1.07)	11 fewer per 1,000 (from 25 more to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Epirubicin + P	1	RCT	not serious	not serious	not serious	serious [2]	none			not pooled		⊕⊕⊕◯ MODERATE	CRITICAL
Belotecan	1	RCT	not serious	not serious	not serious	serious [2]	none			not pooled		⊕⊕⊕◯ MODERATE	CRITICAL
Permetrexed + C	1	RCT	not serious	not serious	not serious	not serious	none			not pooled		⊕⊕⊕⊕ HIGH	CRITICAL
Amrubicin + P	1	RCT	not serious	not serious	not serious	serious [2]	none			not pooled		⊕⊕⊕◯ MODERATE	CRITICAL
Toxicity													
Irinotecan	8	RCT	not serious	not serious	not serious	not serious	none			not pooled		⊕⊕⊕⊕ HIGH	IMPORTANT
Topotecan	3	RCT	not serious	not serious	not serious	not serious	none			not pooled		⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment								№ of patients		Effect		Quality	Importance
Platinum other	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum Etoposide	Platinum other	Relative (95% CI)	Absolute (95% CI)		
Epirubicin + P	1	RCT	not serious	not serious	not serious	serious [2]	none			not pooled		⊕⊕⊕◯ MODERATE	IMPORTANT
Belotecan	1	RCT	not serious	not serious	not serious	serious [2]	none			not pooled		⊕⊕⊕◯ MODERATE	IMPORTANT
Permetrexed + C	1	RCT	not serious	not serious	not serious	not serious	none			not pooled		⊕⊕⊕⊕ HIGH	IMPORTANT
Amrubicin + P	1	RCT	not serious	not serious	not serious	serious [2]	none			not pooled		⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of Life-													
Irinotecan	1	RCT	not serious	not serious	not serious	serious [2]	none			- not pooled		⊕⊕⊕◯ MODERATE	IMPORTANT
Topotecan	1	RCT	not serious	not serious	not serious	serious [2]	none			not pooled		⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations: C = carboplatin; CI = confidence interval; ES = extensive-stage; P = cisplatin; RCT = randomized controlled trial; SCLC = small cell lung cancer

Figure 4-1. Overall survival for irinotecan vs. etoposide and topotecan vs. etoposide for ES SCLC.



In total, three trials compared platinum-topotecan versus platinum-etoposide. Data for overall survival from these trials of moderate aggregate quality were included in a meta-analysis [23-25]. Patients who received topotecan did not have longer overall survival compared with those who received etoposide (HR, 0.97; 95% CI, 0.87 to 1.07; p=0.55). There was no evidence of heterogeneity (X^2=1.98 [df =2], p=0.37). The overall survival at 12 months was estimated by visual inspection from each of the Kaplan-Meier curves and the median of the overall survival at 12 months was 36%; therefore, the baseline risk of mortality was estimated to be 64%. At 64% risk of mortality, there would be 1.1% (11 per 1000) fewer deaths at 12 months (95% CI from 25 more to 51 fewer) for patients in the platinum-etoposide arm.

A test for subgroup differences between irinotecan and topotecan revealed no statistically significant difference (X^2=1.68, p=0.19). Overall, a benefit was shown for irinotecan-topotecan versus etoposide (HR, 0.88; 95% CI, 0.80 to 0.97; p=0.008). There was evidence of statistical heterogeneity (I^2=48%, X^2 =17.25 [df =9]; p=0.04).

Four trials compared other chemotherapy combinations versus platinum-etoposide that were not included in the overall survival meta-analyses [63,78,88,90]. In one trial, pemetrexed-carboplatin was compared with carboplatin/etoposide and was found to be significantly inferior to carboplatin-etoposide [88]. Sun et al. compared amrubicin-cisplatin to cisplatin-etoposide and found that the median survival was greater in the amrubicin-cisplatin group; however, these results were non-significant [90]. Lastly, two trials found their experimental groups cisplatin-epirubicin [63] and belotecan-cisplatin [78] to be comparable to the cisplatin-etoposide group.

In total, eight trials compared platinum-irinotecan versus platinum-etoposide for toxicity for patients with ES SCLC [21,22,26-31]. In patients receiving irinotecan-platinum, there were significantly fewer reported cases of neutropenia [21,26], anemia [26,29], thrombocytopenia [21,26,27,29,30], and febrile neutropenia [26], and significantly more reported cases of diarrhea [22,27-29]. A large study conducted by Kim et al. found that there were significantly more frequent grade 3/4 anemia and nausea in the irinotecan-platinum group [22].

Three trials compared topotecan-cisplatin with cisplatin-etoposide [23-25]. In one trial, patients received oral topotecan with IV cisplatin and found that patients had higher rates of leukopenia, thrombocytopenia, and anemia in the oral topotecan group [23]. In two large studies in which patients received topotecan-cisplatin, there were significantly fewer cases of neutropenia [24], anemia [24], and leukopenia [25]. There were more cases of thrombocytopenia in one trial [24] and fewer in the other trial [25].

Four trials compared toxicities in other chemotherapy combinations versus platinum-etoposide [63,78,88,90]. A large trial conducted by Socinski et al. compared permetrexed-carboplatin with carboplatin-etoposide and found that patients in the permetrexed group had significantly less neutropenia, leukopenia, and febrile neutropenia, and significantly more anemia [88]. Another large trial by Sun et al. compared amrubicin/ciplatin with cisplatin-etoposide and found higher rates of leukopenia, neutropenia, and thrombocytopenia in patients receiving amrubicin-cisplatin [90]. Oh et al. found significantly higher rates of anemia and thrombocytopenia in patients receiving belotecan-cisplatin compared with cisplatin-etoposide [78].

Two trials reported on quality of life and found there were no difference between groups, suggesting that quality of life was not compromised based on the arm to which patients were randomized [23,27].

Non-platinum vs. platinum-etoposide

The characteristics and outcomes of the included studies comparing the platinum-etoposide versus non-platinum are presented in Table 4-10. Two full publications reported data on patients with LS SCLC or ES SCLC [64,91], and two full publications reported data on patients with ES SCLC [77,87].

a) LS-SCLC

In terms of overall survival, the quality of evidence of the randomized controlled trials was moderate (Table 4-11). Aggregate scores of the trials were not possible as the two trials reported on different types of chemotherapy. One trial compared doxorubicin, cyclophosphamide, and etoposide with cisplatin-etoposide and found that the median overall survival was greater in the patients with cisplatin-etoposide [64]. Sundstrom et al. compared epirubicin, cyclophosphamide, and vincristine with cisplatin-etoposide and found that patients receiving cisplatin-etoposide had significantly longer median survival [91].

None of the trials reported on toxicity or quality of life outcomes.

b) ES SCLC

Mixed results were observed in trials comparing platinum-etoposide regimens with non-platinum regimens. Aggregate scores of the trials comparing amrubicin were possible and are reported in Table 4-11. Unfortunately, a meta-analysis was not possible as one was a phase II trial and did not report necessary comparative information. Aggregate scores were not possible as the two trials' experimental arms reported on different types of chemotherapy [64,91]. Therefore, the quality of the individual trial evidence for overall survival can also be found in Table 4-11. The quality of the evidence was moderate for all four trials and was marked down for imprecision as there was either only one study in each group and/or the number of events was lower.

The aggregate overall survival scores of trials comparing amrubicin with cisplatin-etoposide or carboplatin-etoposide were of moderate quality. In one study, the median

overall survival was slightly greater in those receiving carboplatin-etoposide; however, it was not statistically significant [87]. O'Brien et al. conducted a three-arm study comparing amrubicin alone and amrubicin-cisplatin with cisplatin-etoposide, where patients in the amrubicin arms had slightly greater but non-significant overall survival [77]. In the trials comparing other chemotherapy combinations of moderate quality, Baka et al. compared doxorubicin-cyclophosphamide-etoposide with cisplatin-etoposide and found that the median overall survival was slightly greater in patients receiving doxorubicin-cyclophosphamide-etoposide [64]. The trial by Sundstrom et al., however, found that patients receiving cisplatin-etoposide in comparison to cyclophosphamide-etoposide-vincristine had longer median overall survival [91]. The evidence does not support the use of non-platinum-based regimens over platinum-etoposide combinations.

Two moderate-quality trials reported toxicity [77,87]. In one trial, patients who received amrubicin had significantly higher leukopenia and febrile neutropenia when compared with patients receiving carboplatin-etoposide [87]. In this particularly trial, the dose of amrubicin was lowered after two severe infections. In a three-arm study by O'Brien et al., patients receiving either amrubicin or amrubicin-cisplatin had higher grade 3/4 toxicities than patients receiving cisplatin-etoposide [77].

One trial reported on quality of life outcomes, where results revealed better quality of life for those patients in the carboplatin-etoposide arm compared with the amrubicin arm at several time points; however, there were no significant differences [87].

Table 4-10. Studies selected for inclusion for LS SCLC and ES SCLC comparing platinum-etoposide vs. non-platinum

Study or author	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
LS							
Baka et al. 2008 [64] Phase 3 UK April 1999 to Feb 2005	280 pts ≥18 years with max 2 adverse prognostic factors from 2 centres were randomized	ACE (doxorubicin 50 mg/m^2, cyclophosphamide 1 mg/m^2 and E 120 mg/m^2 on D1, followed by oral E 240 mg/m^2 for 2 days) for 3 weeks, 6 cycles	84	ACE vs. PE: Median: 10.9 vs. 12.6 mths, p=0.58 1 yr OS: 44% vs. 54%, p=0.2 2 yr OS: 19% vs. 16%, p=nr	NR	NR	Combination of PE should remain as standard and further studies on anthracycline-based regimens are not warranted.
		PE (80 mg/m^2 D1; 120mg/m^2 D1; followed by oral E 240 mg/m^2 for 2 days), for 3 weeks, 6 cycles	81				
Sundstrom et al. 2002 [91] Phase III Norway Jan 1989-Aug 1994	440 pts between the age of 18-75, ECOG PS 0-2 were randomized. LS pts underwent RT between 3rd or 4th chemo cycle: 15 fx of 2.8 Gy once daily (total, 42 Gy)	CEV: D1 (epirubicin 50mg/m^2, cyclophosphamide 1000mg/m^2, vincristine 2mg); 3 weeks for 5 cycles	109	CEV vs. PE Median: 9.7 mths vs. 14.5 mths, p=0.001 2 OS: 8% vs. 25%, p 5 OS: 3% vs. 10%, p=0.001	NR	NR	EP regimen proved superior to the CEV regimen, with prolonged median and OS survival.
		PE 75 mg/m^2; 100 mg/m^2 D1) + daily E 200 mg/m^2 D2-4; 3 weeks for 5 cycles	105				
ES: Amrubicin							
Sekine et al. 2014 [87] Phase III Japan July 2006-Sept 2007	62 no previous chemo, ECOG PS 0-2 and age ≥70 yrs and life expectancy ≥2 mths, were randomized.	Amrubicin: 40-45 mg/m^2 (70-74 yrs old) or 40 mg/m^2 (≥75 yrs old) D1-3, every 3 wks for 4-6 cycles. Dose was modified after 2 severe infections afterwards pts received 40 mg/m^2	32	A vs. CE: Median OS 10.9 (95% CI 8.4-12.9) vs. 11.3 (9.6-14.9), p=0.735 HR 0.87 (95% CI 0.51-1.48)	A vs. CE, grade ≥3 (%) Leukopenia 78 vs. 47, p=0.017 Neutropenia 91 vs. 80, p=0.294 Febrile neutropenia 34 vs. 3, p=0.003 Lymphopenia: 34 vs. 13, p=0.076 Thrombocytopenia: 19 vs. 23, p=0.759 Anemia: 25 vs. 23, p=1.0	Scores of LCS of the FACT-L and the Eq-5D utility index in CE arm indicated better QoL on several time points, but no sig differences[1].	Amrubicin monotherapy at 40-45 mg/m^2 was toxic and intolerable in elderly Japanese pts.
		CE (AUC=5 D1; 80mg/m^2 D1-3), every 3 weeks for 4-6 cycles	30				

Study or author	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
O'Brien et al. 2011 [77] 5 countries and 16 centres Nov 2006-July 2009	99 patients with WHO PS 0-2, measurable disease according to RECIST v1, age ≥18 years, no prior systemic chemo, and no RT within 14 days, were randomized into 1 of 3 arms.	Arm 1: 3 weekly cycles of amrubicin (45 mg/m^2, D1-3)	30	A vs. PA vs. PE Median OS: 11.1 mths (7.9-14.5) vs. 11.1 mths (7.3-16.3) vs. 10 mths (9.2-13.3)	Grade 4 (%), A vs. PA vs. PE Neutropenia 46.7 vs. 51.5 vs. 37.5 Thrombocytopenia 3.3 vs. 6.1 vs. 0 Anemia 3 vs. 3 vs. 0 Febrile neutropenia 3.3 vs. 3.0 vs. 0 P=nr for all	NR	Amrubicin proved to be an active and well tolerated drug, probably the most active single agent to date. However, it also confirmed that PE is a robust regimen that will remain standard therapy
		Arm 2: 3 weekly cycles of cisplatin (60 mg/m^2 D1) + amrubicin (40 mg/m^2 D1-3)	33				
		Arm 3: 3 weekly cycles of cisplatin (75 mg/m^2, D1) + etoposide (100 mg/m^2 D1, oral 200 mg/m^2 D2-3) or etoposide 100 mg/m^2 for 3 days	32				
Extensive Stage- Other							
Baka et al. 2008 [64] Phase III UK Aprl 1999 to Feb 2005	280 pts ≥18 years with max 2 adverse prognostic factors from 2 centres were randomized	ACE (doxorubicin 50 mg/m^2, cyclophosphamide 1 g/m^2 and E 120 mg/m^2 on D1, followed by oral E 240 mg/m^2 for 2 days) for 3 weeks, 6 cycles	54	ACE vs. PE: Median survival: 8.3 vs. 7.5 mths 1 yr OS: 17% vs. 15% 2 yr OS: 0% vs. 3%	NR	NR	Combination of PE should remain as standard and further studies on anthracycline-based regimens are not warranted.
		PE (80 mg/m^2 D1; 120mg/m^2 D1; followed by oral E 240 mg/m^2 for 2 days), for 3 weeks, 6 cycles	60				
Sundstrom 2002 [91] Phase III Norway Jan 1989 to Aug 1994	440 ES and LS pts between the age of 18-75, ECOG PS 0-2 were randomized.	CEV D1 (epirubicin 50 mg/m^2, cyclophosphamide 1000 mg/m^2, vincristine 2 mg); 3 weeks for 5 cycles	109	CEV vs. PE Median: 6.5 mths vs. 8.4 mths, p=nr 2 OS: 4% vs. 4% 5 OS: 1% vs. 2%	NR	NR	No significant difference in median survival time and OS between groups.
		PE 75 mg/m^2; 100 mg/m^2 D1) + daily E 200 mg/m^2 D2-4; 3 weeks for 5 cycles	113				

Abbreviations: A= amrubicin; ACE = doxorubicin, cyclophosphamide, etoposide; AUC = area under the curve; CE = carboplatin/etoposide; CEV = cyclophosphamide, etoposide, vincristine; D = day; E = etoposide; ES = extensive-stage; ECOG = Eastern Cooperative Oncology Group; fx = fractions; HR = hazard ratio; LS = limited-stage; NR = not reported; OS = overall survival; PA = cisplatin/amrubicin; PE = cisplatin/etoposide; PS = performance status; RT = radiotherapy; SCLC = small cell lung cancer; WHO = World Health Organization

[1]Values of scores given in chart were hard to accurately identify

Table 4-11. Quality of evidence for LS SCLC and ES SCLC comparing platinum-etoposide vs. non-platinum

Quality assessment								Quality	Importance
Non-Platinum agent	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
LS: Overall Survival									
ACE	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
CEV	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
ES: Overall Survival									
Amrubicin	2	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	CRITICAL
ACE	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
CEV	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
ES: Toxicity									
Amrubicin	2	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
ES: Quality of Life									
Amrubicin	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations: ACE = doxorubicin, cyclophosphamide, etoposide; CEV = cyclophosphamide, etoposide, vincristine; ES = extensive-stage; LS = limited-stage; RCT = randomized controlled trial; SCLC = small cell lung cancer

1. Only one study and number of events is lower
2. Number of events is lower

Platinum-Etoposide + Other agent vs. Platinum-Etoposide

The characteristics and outcomes of the included studies comparing the platinum-etoposide versus platinum-etoposide and another agent are presented in Table 4-12. One full publication reported on LS SCLC, one full publication reported on LS SCLC or ES SCLC, and two full publications and one abstract reported on ES SCLC [68,74-76,79].

a) LS SCLC

In terms of overall survival, the quality of evidence of the randomized controlled trials was moderate (Table 4-13). Aggregate scores of the trials were not possible as the two trials reported on different types of chemotherapy. One trial of high-quality evidence comparing tamoxifen-cisplatin-etoposide vs. cisplatin-etoposide found that patients receiving cisplatin-etoposide had higher median and three-year overall survival [75]. Another trial of moderate quality that compared the addition of paclitaxel to cisplatin-etoposide with cisplatin-etoposide alone had slightly better median overall survival in the paclitaxel plus cisplatin-etoposide arm [74].

One trial reported on toxicity and found toxicity profiles to be relatively the same between patients receiving tamoxifen plus cisplatin-etoposide versus those receiving cisplatin-etoposide [75].

There were no trials reporting on quality of life.

b) ES SCLC

Aggregate scores of the trials comparing paclitaxel were possible and are reported in Table 4-13. Unfortunately, a meta-analysis was not possible as one of the trials was much larger than the other trial and it would overshadow the effect of the smaller trial. Aggregate scores were not possible for two trials because the experimental arm reported on different types of chemotherapy [68,79]. The quality of the individual trial evidence for overall survival is also reported in Table 4-13. The quality of the evidence was low to moderate for the trials and was downgraded for risk of bias because of abstract publication and/or imprecision as there was either only one study in each group and/or the number of events was lower.

Two trials of moderate quality compared paclitaxel plus cisplatin-etoposide with cisplatin-etoposide [68,74]. One trial showed that the median overall survival was slightly, but non-significantly higher in the cisplatin-etoposide group in comparison to the paclitaxel plus cisplatin-etoposide group [74]. Results from both Mavroudis et al. and Niell et al. suggested that the addition of paclitaxel to the standard doses of cisplatin-etoposide did not improve overall survival [74,76]. Similarly, another study compared palifosfamide-cisplatin-etoposide with carboplatin-etoposide alone and found that the addition of palifosfamide to carboplatin-etoposide did not improve overall survival [68]. On the other hand, Pujol et al. found that the addition of 4'epidoxorubicin-cyclophosphamide to cisplatin-etoposide resulted in significantly better overall survival when compared with cisplatin-etoposide [79]. The available evidence does not support the addition of a third agent to platinum and etoposide.

Three trials of low to moderate quality reported on toxicity [68,76,79]. Pujol et al. (2001) found that the addition of 4'epidoxorubicin-cyclophosphamide to cisplatin-etoposide showed significantly higher rates of neutropenia, anemia, and thrombocytopenia in those receiving 4'epidoxorubicin-cyclophosphamide compared with cisplatin-etoposide [79]. Niell et al. found higher rates of lymphocytopenia in those receiving paclitaxel plus cisplatin-etoposide compared with those receiving cisplatin-etoposide [76]. Jala et al. found slightly

higher rates of febrile neutropenia in patients receiving carboplatin-etoposide compared with palifosfamide plus carboplatin-etoposide [68].

One trial reported on quality of life and found that patients receiving 4'epidoxorubicin-cyclophosphamide plus cisplatin-etoposide had a significantly higher quality of life from start to end of treatment when compared with those receiving cisplatin-etoposide [79].

Table 4-12. Studies selected for inclusion for LS SCLC and ES SCLC comparing platinum-etoposide vs. platinum etoposide plus other agent

Study or author	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
LS							
McClay et al. 2005 [75] US Aug 1993-Jan 1999	319 pts aged 18 and older, PS 0-2, and no prior chemo, RT, or immunotherapy, were randomized. All patients underwent RT (50 Gy/25 fx) during cycle 4 and 5.	Tamoxifen (80 mg/m^2 orally 2×/day D1-5) + PE (80 mg/m^2 D2; 80 mg/m^2 D2-4), repeated every 3 wks for 5 cycles	153	TAM+ PE vs. PE Median: 18.4 mths (16.4-22.0) vs. 20.6 mths (17.0-24.7) p=nr 3 OS: 25% (19-33) vs. 30% (23-28) p=nr	TAM+PE vs. PE Nausea = 0% vs. 1% Vomiting 5% vs. 4% Infection 2% vs. 1%	NR	TAM+ PE failed to have a clinically meaningful impact on OS.
		PE (80 mg/m^2 D1; 80 mg/m^2 D2-3), repeated every 2 weeks for 5 cycles	154				
Mavroudis et al. 2001 [74] Greece July 1997-March 1999	133 pts with no prior chemo, age 18-75, WHO PS ≤2 were randomized. LS pts additionally received RT (50 Gy/25 fx) after chemo	TEP: paclitaxel (175 mg/m^2 D1)-cisplatin (80 mg/m^2 D2)-etoposide (80 mg/m^2 D3-4), repeated every 28 days with a max of 6 cycles	29	TEP vs. PE: Median: 14 mths (0.5-24) vs. 12.5 mths (1-25), p=nr 1 OS: 58.6% vs. 55%, p=nr	NR	NR	TEP combination at drug doses in study appear to have no additional benefit compared with PE
		PE (80 mg/m^2 D1; 120 mg/m^2 D1-3), repeated every 28 days with a max of 6 cycles	30				
ES: Paclitaxel							
Mavroudis et al. 2001 [74] Greece July 1997-March 1999	133 pts with LS or ES, no prior chemotherapy, age 18-75, WHO PS 2 were randomized.	TEP: paclitaxel (175 mg/m^2 D1)-cisplatin (80 mg/m^2 D2)-etoposide (80 mg/m^2 D2-4], max 6 cycles	33	TEP vs. PE: Median: 7 mths (0.5-27) vs. 9.5 (1-30), p=nr 1 OS: 19.7% vs. 24.4%, p=nr	NR	NR	TEP combination at drug doses in study appear to have no additional benefit compared with PE
		PE (80 mg/m^2 D1; 120 mg/m^2 D1-3), max 6 cycles	41				
Niell et al. 2005 [76] Phase III US April 1998-July 2001	587 pts were ≥18 years old, ECOG PS 0-2, life expectancy greater than 2 mths with no prior chemo or pelvic, mediastinal RT, and non-pregnant for women, were randomized.	TEP: paclitaxel (175 mg/m^2 D1) + PE (80mg/m^2 D1; 80 mg/m^2 D1-3) + G-CSF (D4-18), every 3 wks for 6 cycles	283	TEP vs. PE Median (mths): 10.6 (9.9-11.2) vs. 9.9 (9.2-10.8), p =0.169 1 OS: 38% vs. 37%, p=nr 2 OS: 11% vs. 8% p=nr 3 OS: 4% vs. 4% p=nr	TEP vs. PE (%) Neutropenia 31 vs. 39 Lymphocytopenia 16 vs. 8 Hemoglobin 1 vs. 1 Thrombocytopenia 7 vs. 5	NR	Addition of paclitaxel to standard doses of PE did not improve OS and is not recommended for routine treatment of pts.
		PE (80 mg/m^2 D1; 80 mg/m^2 D1-3), every 3 wks for 6 cycles.	282				

Study or author	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
ES: Other							
Jalal 2015 [68] abstract US unknown years	188 chemo-naïve pts with ES were randomized.	PaCE: palifosfamide (130 mg/m^2) + CE (AUC=4mg D1; 100 mg D1-3)[1]	94	PaCE vs. CE Median OS: 10.0 mths (7.7-10.5) vs. 10.4 mths (8.7-13.4), p=0.096	PaCE vs. CE: Febrile neutropenia 4.3% vs. 5.5%	NR	The addition of PA to CE did not improve survival
		CE (AUC=5mg D1; 100 mg/m^2 D1-3)[1]	94				
Pujol 2001 [79] Phase III March 1996-March 1999	226 pts with WHO PS 0-2, aged below 75 yrs and weight loss of 10% or less during past 3 mths were randomized	PCDE: 4'-epidoxorubicin (40 mg/m^2 D1) + cyclophosphamide (400 mg/m^2 D1-3) + PE, repeated every 4 weeks for 6 courses	117	PCDE vs. PE 1 OS: 40% vs. 29% 18 mth OS: 18% vs. 9% Median 10.5 mths vs. 9.3 mths, p=0.0067	PCDE vs. PE (%) Hemorrhage 4 vs. 0, p=0.06 Nausea and vomiting 22 vs. 19, p=0.58 Neutropenia 99 vs. 85, p<0.0001 Anemia 51 vs. 18, p<0.0001 Thrombocytopenia 78 vs. 18, p<0.0001	Global health status using EORTC QLQ C-30 PE: start of treatment vs. end: 53 (48-57) vs. 58 (53-64) PCDE: start of treatment vs. end: 55 (51-59) vs. 61 (56-66) time effect p<0.0002	PCDE yields a higher response rate and better OS than PE
		PE (100 mg/m^2 D2; 100 mg/m^2 D1-3), repeated every 4 weeks for 6 cycles	109				

Abbreviations: AUC = area under the curve; CE = carboplatin/etoposide; chemo = chemotherapy; D = day; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ = European Organization for Research and Treatment of Cancer Quality of Life questionnaire; fx = fractions; mths = months; NR = not reported; OS = overall survival; PaCE = palifosamide/carboplatin-etoposide; PCDE = expoxorubicin/cyclophosphamide; PE = cisplatin/etoposide; PS = performance status; RT = radiotherapy; TAM = tamoxifen; TEP = paclitaxel, cisplatin, etoposide; WHO = World Health Organization

[1] Cycle length not reported

Table 4-13. Quality of evidence for LS SCLC and ES SCLC comparing platinum-etoposide vs. another agent

Quality assessment								Quality	Importance
	#	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
LS: Overall Survival									
Tamoxifen	1	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	CRITICAL
TEP	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
LS: Toxixity									
Tomoxifen	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
ES: Overall Survival									
Paclitaxel	2	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Other	2	RCT	serious [3]	not serious	not serious	serious [2]	none	⊕⊕◯◯ LOW	CRITICAL
ES: Toxicity									
Paclitaxel	2	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Other	2	RCT	serious [3]	not serious	not serious	serious [2]	none	⊕⊕◯◯ LOW	IMPORTANT
ES: Quality of Life									
Other	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations: ES = extensive-stage; LS = limited stage; RCT = randomized controlled trial; SCLC = small cell lung cancer; TEP = paclitaxel, cisplatin, etoposide

1. Number of events is lower and only one study
2. Number of events is lower
3. Jalal et al. 2015 [68] is an abstract

Platinum-Etoposide plus targeted agent vs. Platinum-Etoposide

The characteristics and outcomes of the included studies comparing platinum-etoposide versus platinum-etoposide plus targeted agent are presented in Table 4-14. One full publication reported data on patients with LS SCLC or ES SCLC and five full publications reported data on patients with ES SCLC [70-72,80,83,89].

a) LS SCLC

In terms of overall survival, the quality of evidence of the randomized controlled trial was high (Table 4-15). In this trial, patients received carboplatin-etoposide plus thalidomide or carboplatin-etoposide plus placebo [71]. Patients in the carboplatin-etoposide plus thalidomide group had slightly higher median overall survival; however, the results were non-significant.

There were no trials reporting on toxicity or quality of life.

b) ES SCLC

Aggregate scores of two trials comparing bevacizumab were possible and are reported in Table 4-15. A meta-analysis was not possible because one of the trials was a phase II trial and did not report on necessary comparative information. Aggregate scores were not possible for the remaining trials as the experimental arm reported on different types of chemotherapy [70-72,83]. Therefore, the quality of the individual trial evidence for overall survival, toxicity, and quality of life can also be found in Table 4-15. The quality of the evidence was moderate to high for the trials and was marked down for risk of bias because of abstract publication or imprecision as there was either only one study and/or the number of events was lower.

The aggregate overall survival scores of trials comparing bevacizumab and chemotherapy alone were of moderate quality. In both trials, the median survival was shown to be slightly longer in patients in the chemotherapy-alone group (carboplatin-etoposide or cisplatin-etoposide) in comparison to those receiving chemotherapy and bevacizumab, suggesting that the addition of bevacizumab was not associated with any benefits to overall survival [80,89]. Four other trials compared different types of chemotherapy. Langer et al. found that the addition of obatoclax to carboplatin-etoposide did not yield a significant improvement in overall survival [70]. Lee et al. found that the addition of thaladomide to carboplatin-etoposide was also not associated with significant benefits to overall survival [71]. Lu et al. reported that the addition of rh-endostatin to carboplatin-etoposide does not improve overall survival in ES SCLC patients [72]. Similarly, Rudin et al. found no additional benefit to overall survival with the addition of oblimersen to carboplatin-etoposide [83]. Current evidence does not support the addition of a targeted agent to platinum-etoposide therapy.

Two moderate aggregate quality randomized controlled trials reported on toxicity comparing bevacizumab with chemotherapy alone. Pujol et al. found that patients receiving the bevacizumab had less anemia, a greater neutrophil count decrease, and greater thrombocytopenia [80]. Spigel et al. found that patients receiving bevacizumab had less neutropenia, and greater hypertension and febrile neutropenia [89]. Three other trials compared different types of chemotherapy with the standard therapy alone. It was found that either the addition of obatoclax [70], rh-endostatin [72], or oblimersen [83] revealed similar and acceptable toxicity compared with carboplatin-etoposide alone.

One study reported on quality of life and found that the overall quality of life at four and six weeks was significantly higher in patients receiving carboplatin-etoposide compared with those receiving rh-endostatin and carboplatin-etoposide [72].

Table 4-14. Studies selected for inclusion for LS SCLC and ES SCLC comparing platinum-etoposide vs. platinum-etoposide plus targeted agent

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
LS							
Lee et al. 2009 [71] 79 centers in UK May 2003-Feb 2006	724 LS and ES pts with no previous chemo or RT, age >18, ECOG PS 0-3 and life expectancy greater than 8 weeks were randomized.	CE + thalidomide: CE (AUC=6 D1; 120 mg/m^2 IV D1-2 and 100 mg orally 2×/day or 120 mg/m^2 IV D1 or 100 mg orally 2×/day D2 and 3) + thalidomide capsules (100 mg/d, if well tolerated 150 mg/d after chemo for 1 mth and then 200 mg/d for rest of trial)	177	Thalidomide vs. placebo Median = 13.1 mths vs. 12.1 mths, p=nr HR for death = 0.91 (95% CI 0.73-1.15), p=nr	NR	NR	Thalidomide is not associated with any benefit on OS.
		CE + placebo: CE (AUC=6 D1; 120 mg/m^2 IV D1-2 and 100 mg orally 2×/day or 120 mg/m^2 IV D1 and 100 mg orally 2×/day D2 and 3) + placebo capsules	191				
ES: Bevacizumab							
Pujol et al. 2015 [80] France Sept 2009 to Oct 2011	74 pts with ECOG 0-2, ≤75 yrs old, <10% weight loss in last 3 months and no prior treatment. Each pt received 2 cycles of either PE (80 mg/m^2 D2; 120 mg/m^2 D1-3) or PCDE (30 mg/m^2 4'-epidoxorubicin D1, P 75 mg/m^2 D2, E 75 mg/m^2 D1-3, cyclophosphamide 300 mg/m^2 D1-3) prior to randomization.	Chemo + Bev: Four additional cycles of chemo + Bev (7.5 mg/kg D1 from cycle 3-6, then every following 3 weeks)	37	Chemo + Bev vs. chemo alone Median 11.1mths (95% CI 8.7-14.0) vs. 13.3 (95% CI 9.8-16.6) HR for CT alone= 0.8, 0.5-1.3, p=0.35	Chemo+ Bev vs. chemo alone Grade 3-4 (%) Anemia 8.6 vs. 16.2 Neutrophil count decrease: 42.9 vs. 35.1 Thrombocytopenia 20 vs. 10.8 p=nr for all	NR	Administering Bev after induction chemo is not an option for ES.
		Chemo alone: Four additional cycles of chemo	37				
Spigel et al. 2011 [89] Phase III Years unknown US 44 centers Mar 2007-Aug 2008	Pts with no prior chemo, 18 years or older, and had ECOG PS 0-2 were randomized.	BV: Bev (15 mg/kg D1) + CE (AUC=5 D1; 100 mg/m^2 D1-3) or PE (75 mg/m^2 D1; 100 mg/m^2 D1-3), 4 cycles	52	BV vs. placebo Median 9.4 (95% CI 8.7-11.3) vs. 10.9 (95% CI 8.1-14.7) HR 1.16 (95% CI 0.66-2.04), p=ns	BV vs. placebo (grade 3-4): Neutropenia 35.3 vs. 40.4 Hypertension 5.9 vs. 4.3 Thrombocytopenia 4.3 vs. 4.0 Febrile neutropenia 5.9 vs. 0	NR	Addition of BV to PE or CE did not lead to an improvement in OS
		Placebo: CE (AUC=5 D1; 100 mg/m^2 D1-3) or PE (75 mg/m^2 D1; 100 mg/m^2 D1-), 4 cycles	50				
ES: Other							

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
Langer 2014 [70] Phase II International Multicenter Years unknown	155 chemo-naïve pts who were ≥18 years of age, ECOG PS 0-2 and normal bone marrow, liver and kidney function were randomized.	CEOb = CE (AUC=5 D1; 100 mg/m^2 D1-3) + obatoclax (30 mg D1-3), 21 day cycle for 6 cycles	83	CEOb vs. CE Median 10.5 mths (95% CI 8.9-13.8) vs. 9.7 mths (95% CI 7.2-11.2) HR=0.823, p=0.121 1yr OS: 46% vs. 37%, p=0.117	CEOb vs. CE (%) Neutropenia 46 vs. 47 Thrombocytopenia 18 vs. 15 Anemia 21 vs. 21 Leukopenia 9 vs. 12	NR	The addition of CEOb failed to yield a significant improvement in OS
		CE (AUC=5 D1; 100 mg/m^2 D1-3), 21 day cycles for 6 cycles	82				
Lee et al. 2009 [71] Phase III 79 centers in UK May 2003-Feb 2006	724 LS and ES pts with no previous chemo or RT, age >18, ECOG PS 0-3 and life expectancy greater than 8 weeks were randomized.	CE (AUC 5 D1; 120 mg/m^2 IV D1-2 and 100 mg orally 2x/day or 120 mg/m^2 IV D1 and 100 mg orally 2×/day D2-3) + thalidomide capsules 100 mg/d, if well tolerated 150 mg/d after chemo for 1 mth and then 200 mg/d for rest of trial)	188	Thalidomide vs. placebo Median = 8.0 mths vs. 9.1, p=nr HR for death = 1.36 (95% CI = 1.10-1.68), p=nr	NR	NR	Thalidomide is not associated with any benefit on OS.
		CE (AUC 5 D1; 120 mg/m^2 IV D1-2 and 100 mg orally 2x/day or 120 mg/m^2 IV D1 and 100 mg orally 2x/day D2 and 3) + placebo capsules	168				
Lu et al. 2015 [72] Phase II China 14 centres July 2009-Aug 2011	140 pts between 18-75 yrs old with ECOG PS 0-2 and expected survival of more than 12 wks were randomized	CE (AUC=5 mg/m^2/min D1; 60 mg/m^2 D1-5) + rh-e (7.5 mg/m^2 1× daily D1-14), 4-6 21 day cycles	69	CE+rh-e vs. CE Median: 12.1 mths vs. 12.4 mths, p=0.812 1 yr OS: 50% vs. 54.6% HR = 1.0 (0.7-1.6), p=ns	CE+rh-e vs. CE (%) Leukopenia 29 vs. 21.7, p=0.434 Neutropenia 55.1 vs. 39.1, p=0.088 Hemoglobin 15.9 vs. 10.1, p=0.449 Thrombocytopenia 18.8 vs. 18.8, p=1.00 Anemia 1.4 vs. 2.9, p=1.00	CE+ rh-e vs. CE 2 wk: 5.5 vs. 3.5 4 wk: 2.5 vs. 7.0, p<0.05 6 wk: 2.2 vs. 7.0, p<0.05[1]	Results suggest that the addition of rh-e to CE has acceptable toxicity but does not improve OS
		CE (AUC=5 mg/m^2/min D1; 60 mg/m^2 D1-5)	69				
Rudin et al. 2008 [83] Phase II US Years unknown	63 pts ≥18 years of age with ECOG PS 0-2, and no prior chemo.	Arm A: CE (AUC=5 D6; 80 mg/m^2 D6-8) + oblimersen (7 mg/kg D1-8), 21 day cycle	41	A vs. B Median 8.6% (95% CI 7.2-10.8) vs. 10.6% (95% CI 8.4-17.0) HR = 2.1 (95% CI 1.1-4.1), p=0.02 ≥12 months = 24% (95% CI 12-40) vs. 47% (95% CI 21-73)	A vs. B Grade 3+ (%) Hemoglobin 17 vs. 7 Leukocytes 49 vs. 33 Lymphopenia 5 vs. 13 Neutophils 80 vs. 60 p=nr	NR	The addition of oblimersen to CE was not associated with improvements in OS
		Arm B: CE (AUC=5 D1; 80 mg/m^2 D1-3), 21 day cycle	15				

Abbreviations: AUC = area under the curve; Bev = bevacizumab; BV = bevacizumab/carboplatin-etoposide or cisplatin-etoposide; CE = carboplatin/etoposide; CEOb = obatoclax/carboplatin-etoposide; chemo = chemotherapy; D = day; ECOG = Eastern Cooperative Oncology Group; ES = extensive-stage; HR = hazard ratio; LS = limited-stage; mths

= months; OS = overall survival; PCDE = expoxorubicin/cyclophosphamide; PE = cisplatin/etoposide; PS = performance status; rh-e = rh-endostatin; RT = radiotherapy; SCLC = small cell lung cancer

[1] Values estimated from graph

Table 4-15. Quality of evidence for LS SCLC and ES SCLC comparing platinum-etoposide vs. targeted agent

Quality assessment								Quality	Importance
Targeted Agent	# of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
LS: Overall Survival									
Thalidomide	1	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	CRITICAL
ES: Overall Survival									
Bevacizumab	2	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
CEOb	1	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Thaladomide	1	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	CRITICAL
Rh-endostatin	1	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Oblimersen	1	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	CRITICAL
ES: Toxicity									
Bevacizumab	2	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
CEOb	1	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Rh-endostatin	1	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Oblimersen	1	RCT	not serious	not serious	not serious	serious [2]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
ES: Quality of Life									
Rh-endostatin	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviation: CEOb = obatoclax/carboplatin-etoposide; ES = extensive-stage; LS = limited-stage; RCT = randomized controlled trial; SCLC = small cell lung cancer; TEP = paclitaxel, cisplatin, etoposide

1. Number of events is lower
2. Number of events is lower and only one study

Maintenance versus no maintenance

The characteristics and outcomes of the included studies comparing maintenance versus no maintenance are presented in Table 4-16. No trials reported on patients with LS SCLC and four full publications reported data on patients with ES SCLC [66,67,82,85]. Aggregate scores were not possible for the trials reporting on various maintenance therapies. Therefore, the quality of the individual trial evidence for overall survival, toxicity, and quality of life can

also be found in Table 4-17. The quality of the evidence was moderate and was marked down for imprecision as there was only one study and the number of events was lower.

There were four moderate-quality randomized controlled trials comparing maintenance therapy and no maintenance therapy. Han et al. compared irinotecan maintenance with observation and found that the median overall survival was lower for patients in the maintenance group [66]. Similarly, Schiller et al. found that topotecan maintenance therapy did not result in significant overall survival benefit [85]. A phase II study comparing sunitinib as the maintenance therapy found that overall survival was greater in the maintenance therapy group; however, results were not statistically significant [82]. Hanna et al. (2002) had similar results with etoposide maintenance therapy, where the overall survival was slightly longer than the observation group but the results were not statistically significant [67].

Four moderate-quality studies reported on toxicity [66,67,82,85]. Depending on the type of maintenance therapy used, there was an increase in the percentage of fatigue, neutropenia, anemia, and thrombocytopenia among the patients who received maintenance treatment.

One trial reported on quality of life and found that there was no significant difference in quality of life over four months in patients receiving topotecan as a maintenance therapy and those in the observation group [85].

Platinum-topoisomerase inhibitor versus other regimen

The characteristics and outcomes of the included studies comparing a platinum-topoisomerase inhibitor with other agents are presented in Table 4-18. No trial reported data on patients with LS SCLC and five full publications and one abstract reported data on patients with ES SCLC [65,73,81,84,86,92]. A meta-analysis was not possible because one of the trials was a phase II trial and did not report on necessary comparative information. Aggregate scores of the trials comparing amrubicin were possible and are reported in Table 4-19. Aggregate scores were not possible for the remaining trials as the experimental arm reported on different types of chemotherapy. The individual trial quality of the evidence for these trials can also be found in Table 4-19. The quality of the evidence ranged from low to high and was downgraded for risk of bias as one was an abstract and imprecision as there was only one study resulting in the number of events being lower.

The aggregate overall survival scores of trials comparing amrubicin-cisplatin and irinotecan-cisplatin were of moderate quality [65,84]. In both trials, the median survival was shown to be longer in patients receiving irinotecan-cisplatin when compared with those receiving amrubicin-cisplatin; however, these results were non-significant. Similarly, a trial by Sekine et al. found that patients receiving irinotecan-cisplatin has slightly longer overall survival compared with those receiving irinotecan-cisplatin and etoposide [86]. Tamiya et al. found that patients receiving amrubicin-irinotecan had similar median and one-year overall survival compared with patients receiving irinotecan-cisplatin [92]. Quoix et al. found that patients receiving either topotecan-etoposide or topotecan-cisplatin had similar median overall survival [81]. Lyss et al. found that patients receiving pacilitaxel-topotecan had a longer median overall survival compared with those receiving either paclitaxel-topotecan or topotecan-cisplatin [73]. These trials are all small and underpowered for survival outcomes and therefore should not influence practice.

Five moderate-quality studies reported on toxicity [73,81,84,86,92]. Trials comparing irinotecan-cisplatin with amrubicin-platinum found that there was an increase in the percentage of patients who experience thrombocytopenia, anemia, and leukopenia in the amrubicin-platinum treatment [65,84]. There was mixed results on neutropenia. Similarly, a

trial comparing irinotecan-cisplatin and irinotecan-cisplatin-etoposide found that patients in the irinotecan-cisplatin-etoposide groups experienced significantly greater leukocytopenia, neutropenia, and thrombocytopenia [86]. However, Tamiya et al. found that there were no significant differences in hematological toxicity when comparing amrubicin-irinotecan with irinotecan-cisplatin; however, the rates of vomiting, loss of appetite, and diarrhea increased [92].

Two trials reported on quality of life. Satouchi et al. found that patients in the irinotecan-cisplatin group had slightly greater quality of life compared with those in the amrubicin-cisplatin group [84]. Quoix et al. (2005) found that patients receiving topotecan-etoposide had slighter greater quality of life scores compared with those receiving topotecan-cisplatin. Both groups showed a slight increase in quality of life scores with each chemotherapy course; however, this difference was not statistically significant [81].

Table 4-16. Studies selected for inclusion for ES SCLC comparing maintenance vs. no maintenance

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Authors' Conclusions
Han et al. 2008 [66] Phase II Korea March 2003-Apr 2006	120 pts with ECOG PS 0-2, ≥18 years, and no prior RT or chemo were treated with IP (60 mg/m^2 D1,8,15; 30 mg/m^2 D1 & 8), 28 day cycle for max 6 cycles or IP (60 mg/m^2 D1 & 8; 30 mg/m^2 D1 & 8), 21 day cycle, max 8 cycles. Responding patients were randomized.	Arm A: Irinotecan maintenance (100 mg/m^2) D1,8,15. Every 4 wk x6 cycles.	21	A vs. B Median: 17.6 (95% CI 16.4-18.8) vs. 20.5 (95% CI 12.5-28.5) p=nr 1 yr OS (%): 85.7 (95% CI 70.8-100) vs. 83.3 (95% CI 68.4-98.2) p=nr 2 yr OS (%): 19.6 (95% CI 0.6-38.6) vs. 33.7 (95% CI 11.7-55.7), p=nr	All pts (n=119; %), Grade 3-4 Neutropenia 63.9 Anemia 24.3 Thrombocytopenia 8.4 Maintenance chemo pts[1] Neutropenia 28.6 Anemia 28.6 Thrombocytopenia 0	NR	Maintaining with irinotecan as a single therapy after 6-8 cycles of IP chemo failed to show any additional survival benefit.
		Arm B: Observation	24				
Hanna et al. 2002 [67] Phase III US Sept1993 - June 1998	233 patients with Karnofsky PS ≥50, adequate bone marrow reserve/renal function received etoposide 75 mg/m^2 D1-4, cisplatin 20 mg/m^2 D1-4, and ifosfamide 1.2 g/m^2 D1-4 with Mesna. Course was repeated every 3 wks for 4 cycles. Pts with CR, PR, or SD were randomized.	Arm A: Etoposide 50 mg/m^2 D1-22 every 4 wks × 3	72	A vs. B Median 12.2 vs. 11.2 mths p=nr 1 OS 51.4% vs. 40.3%, 2 OS 16.7% vs. 6.9% 3 OS 9.1% vs. 1.9% p=nr	Grade 3/4 toxicity (n) Anemia 14 Leukopenia 26 Granulocytopenia 30 Thrombocytopenia 14	NR	Toxicity of oral etoposide was minimal and suggested an improved OS with maintenance oral etoposide.
		Arm B: Observation	72		NR		
Ready et al. 2015 [82] Phase II US Mar 2007-Dec 2011	144 pts with ECOG PS 0-2 received PE induction (80 mg/m^2 D1; 100 mg/m^2 D1-3; every 21 days; up to 6 cycles). Pts with CR, PR, or SD were randomized	Sunitinib (150 mg D1 and then 37.5 mg per day) until progression. Initiated at least 3 wks, but no later than 8 wks after D1 of last chemo cycle.	44	Sunitinib vs. placebo Median: 9.0 mths (8.0-12.7) vs. 6.9 mths (5.4-11.8) 1 OS: 36.0% (22.0-50.3) vs. 33.6% (19.7-48.1) HR = 1.28 (0.79-2.10), p=0.16	≥3 toxicity (%) Fatigue: 19 Neutrophils 14 Leukocytes 7 Platelets 7	NR	OS was greater in sunitinib maintenance, but was not statistically significant.
		Placebo until progression. Initiated at least 3 wks, but no later than 8 wks after D1 of last chemo cycle.	41		≥3 toxicity (%) Fatigue 10 Platelets 2 Hypernatremia 2		
Schiller et al. 2001 [85] Phase III US March 1995-Jan 1999	420 pts over 18 years old, ECOG PS 0-2 with adequate hematologic/ hepatic/renal function and no prior chemo. All pts underwent 4 cycles PE (60 mg/m^2 D1; 120 mg/m^2 D1-3; 21 days cycle). Pts with SD or CR/PR were stratified.	Arm A: Topotecan: 1.5 mg/m^2 for 5 days every 21 days, 4 cycles	112	A vs. B Median: 9.3 (95% CI 8.6-10.0) vs. 8.9 (95% CI 7.7-10.0), p=nr 1 yr OS (%) = 25 vs. 28 2 yr OS (%)= 8 vs. 6 p=nr RR=1.13 (95% CI 0.85-1.47), p=0.43	Topotecan vs. observation (grade 4): White blood count: 12 vs. 0 Hematocrit 3 vs. 0 Nausea 0 Infection 2 vs. 0	FACT-L questionnaire: no significant difference over 4 mths scores between arms.	4 cycles of topotecan after 4 cycles of PE did not result in significant benefit compared with PE
		Arm B: Observation	111				

							alone.

Abbreviations: Chemo = chemotherapy; CR = complete response; D = day; ECOG = Eastern Cooperative Oncology Group; FACT-L = Functional Assessment of Cancer Therapy – Lung; HR = hazard ratio; IP = irinotecan-cisplatin; OS = overall survival; PE = cisplatin-etoposide; PR = partial response; PS = performance status; pts = patients; QoL = quality of life; RR = relative risk; RT= radiotherapy; SD = stable disease

[1] Toxicity scores for pts in observation group not reported

Table 4-17. Quality of evidence for ES SCLC comparing maintenance vs. no maintenance

Quality assessment								Quality	Importance
Maintenance Therapy	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
ES: Overall Survival									
Irinotecan	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Etoposide	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Sunitinib	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Rh-endostatin	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
ES: Toxicity									
Bevacizumab	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
CEOb	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Rh-endostatin	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Oblimersen	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
ES: Quality of Life									
Rh-endostatin	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations: CEOb = obatoclax/carboplatin-etoposide; ES = extensive-stage; RCT = randomized controlled trial; SCLC = small cell lung cancer; TEP = paclitaxel, cisplatin, etoposide

1. Number of events is lower and only one study

Table 4-18. Studies selected for inclusion for ES SCLC comparing platinum-topoisomerase inhibitor vs. other

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Conclusions
Amrubicin							
Fujita et al. 2015 [65] *abstract* Phase II *unknown* Dec 2009-March 2013	71 chemo-naive pts were randomized	CA: carboplatin (AUC 4.0 D1) + amrubicin (35 mg/m^2 D1-3), every 3 weeks	~35[1]	CI vs. CA: Median 12.2 mths vs. 15.9 mths HR (CA) = 0.77 (95% CI 0.49-1.29, p=0.318	CI vs. CA, Grade3+ (%) Neutropenia: 53 vs. 89 Anemia 26 vs. 20 Thrombocytopenia 18 vs. 14 Febrile neutropenia 12 vs. 29	NR	Carboplatin/amrubicin was numerically effective with acceptable toxicity.
		CI: carboplatin (AUC 5 D1) + irinotecan (70 mg/m^2 D1, D8), every 3 weeks	~35[1]				
Satouchi et al. 2014 [84] Phase III Japan May 2007-December 2010	284 chemo-naïve pts, aged 20-70 yrs, ECOG PS 0-1, no prior chemo or RT, and adequate organ function.	AP: amrubicin 40 mg/m^2 D1-3); cisplatin (60 mg/m^2 D1, 3 wks. Amrubicin dose was reduced to 35 mg/m^2 due to high toxicity (after 66% were enrolled)	142	AP vs. IP[3] Median 15.0 mths (13.5-17.5) vs. 17.7 mths (14.0-22.1) HR = 1.43 (1.10-1.85), p=ns 1 yr OS 63.9 vs. 68.3 2 yr OS 21.7 vs. 39.2 p=nr	AP vs. IP, grade 3-4 (%) Leukopenia 79.3 vs. 22.5 Neutopenia 95.7 vs. 58.4 Anemia 36.5 vs. 23.2 Thrombocytopenia 27.1 vs. 2.1	QoL-ACD Physical status (AP vs. IP) 31.7% vs. 37.1% OR 0.72 (0.43-1.22), p=0.23	IP showed favourable OS and toxicity.
		IP: irinotecan (60 mg/m^2 D1,8,15); cispatin (60 mg/m^2 D1), 4 weeks	142				
Other							
Lyss et al. 2002 [73] Phase II US April 1995-October 1997	57 pts with PS 0-2 (except arm 4), life expectancy >2 mths and lack other serious comorbidity and age ≥16 years, were randomized[2]. G-CSF was given at 5 µg/kg on 6th day.	Arm 3: Paclitaxel (230 mg/m^2 D1) + topotecan (1mg/m^2 D1-5), every 21 days/6 cycles	13	Arm 3 vs. 4 vs. 1: Median: 13.8 mths (1.84-infinity) vs. 9.9 (7.57-15.1) vs. 5.74 mths (4.72-infinity) 1 OS: 62% (40-95%) vs. 40% (26-61% vs. 17% (5%-59%)	Grade 4 toxicities experienced by ≥50% inc. granulocytopenia and lymphocytopenia.	NR	Cisplatin/topopotecan and Paclitaxel/topotecan were associated with excessive mortality and toxitiy. PE/CE regimens still the
		Arm 4: Paclitaxel (175 mg/m^2 D1) + toptecan (1mg/m^2 D1-5), every 21 days/6 cycles	32		Grade 3/4 toxicity (%) experienced by >10 % of pts. Lymphocytopenia (69%), granulocytopenia (56%), leukopenia (56%), anemia (28%), thrombocytopenia (25%), hyperglycemia (16%)		
		Arm 1: cisplatin (75 mg/m^2 D1) + topotecan 1mg/m^2 D1-5), every 21	12		Grade 4 toxicities experienced by ≥50% inc. leukopenia,		

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Conclusions
		days/6 cycles			granulocytopenia, thrombocytopenia, lymphocytopenia, gastrointestinal toxicity.		standard for LS and ES.
Quoix et al. 2005 [81] Phase II Canada/Europe Yrs unknown	84 pts aged at least 18 years, ECOG PS 0-2, life expectancy of at least 3 mths, adequate bone, renal and hepatic function were randomized.	Topotecan (0.75 mg/m^2 once daily D1-5) + etoposide (60 mg/m^2 D 1-5 before each topo), every 21 days	41	TE vs. TP Median: 43.7 weeks (10.1 mths) vs. 41.6 wks (9.6 mths), p=nr	TE vs. TP, grade 3/4 (%) Neutropenia: 87.5 vs. 87.8 vs., p ns Leukopenia: 67.5 vs. 39.1, p=ns Thrombocytopenia 20 vs. 31.7, p=ns Anaemia 20 vs. 46.4, p=0.018	FACT-L (max score 84) TE vs. TP: baseline 53.99 (SE 1.73) vs. 50.12 (SE 1.77), mean score tended to show a slight increase with each chemo course, but no statistical difference.	Both TP and TE are effective combination therapies in pts with ES.
		Topotecan (1.25mg/m^2 once daily D 1-5) + cisplatin (50 mg/m^2 on D5 of topo), every 21 days	41				
Sekine et al. 2008 [86] Phase II Japan March 2003-May 2005	110 pts with no prior treatment, ECOG PS 0-2, life expectancy of 3 mths or longer, adequate organ function and between the age of 20-70	IPE: irinotecan (60 mg/m^2 D1 & 8) + cisplatin (60 mg/m^2 D1) + etoposide (50mg/m^2 D1-3), repeated every 3 weeks/4 cycles	55	IP vs. IPE Median: 12.4 mths (95% CI 9.7-15.1) vs. 13.7 mths (95% CI 11.9-15.5) 1 OS 54.8% (95% CI 41.4-68.2) vs. 61.5% (95% CI 48.6-74.4), p=0.52	IP vs. IPE, grade 3/4 (%) Leukocytopenia 19 vs. 53, p<0.001 Neutropenia 52 vs. 95, p<0.001 Anemia 25 vs. 45, p=nr Thrombocytopenia 4 vs. 13, p<0.01 Febrile neutropenia 9 vs. 13, p=nr	NR	IPE regimen was marginally more effective than IP, but too toxic despite G-CSF.
		IP: irinotecan (60 mg/m^2 D1 & 8) and cisplatin (60 mg/m^2 D1), repeated every 3 weeks/4 cycles. No G-CSF support	54				
Tamiya et al. 2015 [92] *abstract* Phase II	100 pts with ECOG PS 0-2, aged 20 or older, pathologically proven ES (LD with pleural effusion were also eligible) and adequate organ function were	AI: Amrubicin 90 mg/m^2 D1; irinotecan 50 mg/m^2 D1, 8), 21 cycle	50	AI vs. IP Median: 14.7 mths vs. 14.2 mths, HR 0.69 (CI and p value NR) 1 yr OS: 68% (95% CI 56.2-82.2) vs.	No significant difference in hematological toxicity, whereas rates of vomiting, loss of appetite, diarrhea, and elevated serum creatinine were more frequent in IP.	NR	AI showed similar efficacy to that of IP, but study did not meet primary endpoint.
		IP: ironotecan (60 mg/m^2 D1, 8, 15), 28 day cycles; cisplatin (60 mg/m^2 D1)	50				

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Conclusions
	randomized.			62.8 (95% CI 50.5-78.0), p=0.29			

Abbreviations: AI = amrubicin/irinotecan; AP = amrubicin/cisplatin; CA = carboplatin-amrubicin; CE = carboplatin/etoposide; CI = carboplatin-irinotecan; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; G-CSF = granulocyte macrophage colony-stimulating factor; HR = hazard ratio; IP = irinotecan/cisplatin; IPE = irinotecan, cisplatin, etoposide; NR = not reported; ns = not significant; OS = overall survival; PE = cisplatin/etoposide; PS = performance status; pts = patients; QoL = quality of life; RT = radiotherapy; TE = topotecan/etoposide; TP = topotecan/cisplatin

[1] Number of patients is approximate as exact number was not reported
[2] Study was initially 3 arm, but due to excessive toxicity, 2 arms were closed and later a 4th arm was added (PS 0-1). Arm 2 was not reported in this article.
[3] The initial dose reduction in amrubicin had no impact on any efficacy results when the dose was reduced to 35 mg.

Table 4-19. Quality of evidence for ES SCLC comparing platinum/topoisomerase inhibitor vs. other

Quality assessment								Quality	Importance
Platinum other	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Overall Survival									
Amrubicin	2	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	CRITICAL
Paclitaxol/topotecan	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Etoposide/topotecan	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Irinotecan/PE	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Amrubicin/irinotecan	1	RCT	serious [2]	not serious	not serious	serious [1]	none	⊕⊕◯◯ LOW	CRITICAL
Toxicity									
Amrubicin	2	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	IMPORTANT
Paclitaxol/topotecan	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Etoposide/topotecan	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Irinotecan/PE	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Amrubicin/irinotecan	1	RCT	not serious [2]	not serious	not serious	serious [1]	none	⊕⊕◯◯ LOW	IMPORTANT
Quality of Life									
Amrubicin	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT
Topotecan/cisplatin	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations: ES = extensive-stage; PE = cisplatin-etoposide; RCT = randomized controlled trial; SCLC = small cell lung cancer

1. Number of events is lower and only one study
2. Abstract

6. *For non-resected patients with LS SCLC or ES SCLC, what is the optimal dose and schedule of chemotherapy with respect to overall survival, quality of life, and toxicity?*

The characteristics and outcomes of the included studies comparing the optimal dose and schedule of chemotherapy are presented in Table 4-20. Two full publications reported data on patients with LS SCLC [14,15] and 10 full publications reported data on patients with

ES SCLC [32-41]. Aggregate scores of the trials were not possible as each trial had different doses and/or schedules. Therefore, the quality of the individual trial evidence for overall survival and toxicity can be found in Table 4-21. The quality of the evidence was moderate to high and was marked down for imprecision when there was only one study and the number of events was lower.

a) LS SCLC

Two moderate-quality trials reported on overall survival that examined varying doses. In a phase III trial conducted by Leyvraz et al., the conventional doses of ifosphamide, carboplatin, etoposide, and uromitexan were compared with high doses of these drugs [14]. No difference was observed in overall survival [14]. Scullier et al. evaluated standard-dose cisplatin-etoposide plus thoracic radiotherapy versus daily low-dose cisplatin and standard-dose etoposide [15]. Overall survival favoured the low-dose cisplatin but this difference was not significant [15]. Patients receiving the daily cisplatin-etoposide had significantly greater thrombocytopenia [15].

No trial reported on quality of life.

b) ES SCLC

One moderate-quality trial compared optimal doses for overall survival and toxicity [32]. In this trial, patients were randomized to conventional carboplatin-etoposide or dose-intensified therapy with carboplatin-etoposide. There were no significant differences between groups for overall survival. Patients receiving the conventional carboplatin-etoposide experienced significantly greater neutropenia and less thrombocytopenia compared with the dose-intensified group.

Nine moderate- to high-quality trials reported on overall survival looking at varying schedules [33-41]. Some trials demonstrated no difference in overall survival whereas others demonstrated improvements in overall survival. The majority of trials were small and not powered to answer questions about overall survival. With respect to trials involving cisplatin-etoposide regimens, Baka et al. found no significant differences in overall survival when patients were randomized to receive either four cycles of cisplatin-etoposide followed by four cycles of topotecan or the same regimens with alternating scheduling [33]. Similarly, Ignatiadis et al. found that sequential and alternating cisplatin-etoposide achieved similar median and oneyear overall survival [34]. Another trial found a trend in overall survival in favour of six-cycle therapy compared with four-cycle therapy [40]. Masutani et al. compared dose-intensive weekly alternating and standard alternating cycles of cyclophosphamide, doxorubicin, and vincristine, finding that the weekly regimen showed significant improvements in survival time [35]. Another study found no significant difference in overall survival between the rapidly alternating sequence of cyclophosphamide, doxorubicin, and vincristine (hybrid chemotherapy) or the sequential chemotherapy groups [39]. Similarly, a trial comparing accelerated versus the standard of epirubicin, vindesine, and ifosfamide found no survival difference with respect to median duration or at two years [37]. A phase II trial of daily versus continuous-infusion schedules of topotecan found that the median survival of the daily infusion group was higher [36]. The continuous infusion schedule was closed early due to insufficient activity [36]. Another phase II study comparing cisplatin-etoposide plus irinotecan administered weekly or every four weeks found that median survival was higher in patients in the weekly schedule [38]. Interestingly, a study comparing irinotecan-cisplatin followed by cisplatin-etoposide and the reverse sequence found overall survival to be similar in both groups [41]. The evidence that dose or intensity of chemotherapy influences overall

survival is weak. However, the question of longer-duration therapy requires further evaluation.

Seven trials reported on toxicity [33-38,41]. The percentage of patients experiencing neutropenia was significantly higher in the daily schedule versus continuous [36], in those receiving chemotherapy every four weeks versus weekly schedule [38], and if receiving cisplatin-etoposide followed by irinotecan-cisplatin [41]. Patients in the daily schedule also experience higher leukopenia [36]. The remaining trials showed similar toxicity between the schedule comparisons.

There were no trials reporting on quality of life.

Ongoing, Unpublished, or Incomplete Studies

A list of ongoing, unpublished, or incomplete studies located in the literature search or from clinicaltrials.gov is given in Appendix 7. This list is not meant to be all-inclusive and it is likely other trials are also ongoing.

Table 4-20. Studies selected for inclusion for LS SCLC and ES SCLC patients comparing optimal dose and schedule of chemotherapy.

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Conclusions
LS: Dose							
Leyvraz et al. 2008 [14] Phase III Europe, 18 centers June 1997 to Dec 2005	145 pts aged <65 yrs, ECOG PS 0-1 with no previous treatment were randomly assigned. Pts underwent thoracic RT(60Gy/2Gy fx)	High dose: 3 cycles (28 days/cycle): ifosfamide 2.5 g/m^2/day × 4 days (10 g/m^2); carboplatin (AUC 5/day × 4 days AUC 20; etoposide: 300 mg/m^2/day × 4 days (1200 mg/m^2); uromitexan: 5.0 g/m^2/day D1-5	49	Group A vs. B: 2 yrs OS = 39% (95% CI 25-53) vs. 37 % (95% CI 23-50), p=0.767	NR	NR	Succeeded in raising the peak dose, total dose and dose intensity but was ineffective, toxic, and costly. This strategy should be abandoned.
		Standard: 6 cycles (28 days per cycle): ifosfamide 5.0 g/m^2 and carboplatin 300 mg/m^2 D1; etoposide 180 mg/m^2 D1- 2; uromitexan 5.0 g/m^2 D1 -2	48				
Sculier et al. 2008 [15] Phase III Europe Mar 1993 to Mar 2006	214 pts undergoing chest irradiation (39.90 Gy/15 fx >3 wks) and chemo. Both started on D1	Group A: PE (90 mg/m^2 D1; 100 mg/m^2 D1-3) + standard induction chemo RT	104	Group A vs. B Median 15.5 mths (95% CI 12.0-18.9) vs. 17.0 (95% CI 13.9-20.0) 2 yr: 35% (95% CI 25-45%) vs. 38% (95% CI 28-48%) 5 yr: 18% (95% CI 10-26%) vs. 21% (95% CI 13-29%) HR = 0.89 (95% CI 0.65-1.22), p=0.48	Grade 3/4 (A vs. B), % Infection = 8 vs. 14, p=0.25 Alopecia = 46 vs. 38, p=0.31 Leukopenia= 90 vs. 87, p=0.51 Thrombocytopenia = 33 vs. 59, p<0.001 Esophagitis: 4 vs. 8, 0.40	NR	Induction chemo RT with the PE regimen and chest irradiation administered during the 1st cycle of chemo resulted in good long-term survival.
		Group B: PE (6 mg/m^2 D1-4, D8-12, D15-90; 90 mg/m^2 D1; E = 100 mg/m^2 D1-3) + daily chemo RT	100				
ES: Dose							
Heigener et al. 2009 [32] Germany Jan 2000 to Dec 2003	79 pts between 18-75 yrs with no prior chemo or RT, ECOG 0-2 and life expectancy >3 months were randomized	Arm A: CE (AUC 5 D1; 140 mg/m^2 D1-3), repeated every 28 days	37	A vs. B: Median = 11.2 mths (95% CI 9.1-15.2) vs. 11.9 mths (95% CI 8.8-14.7), p=nr	Grade 3/4 (A vs. B), % Anemia= 19.4 vs. 32.5, p=0.096 Neutropenia: 69.4 vs. 37.5, p=0.009 Thrombocytopenia: 28.9 vs. 62.5, p=0.032 Fatigue 27.0 vs. 35.0, p=0.45 Infection 12.1 vs. 5.6, p=0.34	NR	No statistical difference in OS between the 2 arms.
		Arm B (dose intensified): CE (AUC 5 D1; (190 mg/m^2 D1-3) with lenograstim (263 µg D4-13), repeated every 21 days	42				
ES: Schedule							
Baka et al. 2010 [33] Phase III locations NR	370 pts from multiple hospitals aged >18 with a WHO PS 0-1 and no prior	Arm A: PE regimen (80 mg/m^2 D1; 100 mg/m^2 D1-3) 21 days, cycles 1,3,5,7 and topotecan (1.5 mg/m^2/d for 5 days) every 21 days, cycles 2, 4, 6, and 8	184	A vs. B: Median = 9.8 months (range 0.5-86.1) vs.10.9 mths (range 0.5-86.2)	Grade 3/4 (%), A vs. B Anemia 11.6 vs. 13.1, p =0.461 Neutropenia 54.7 vs. 55.8, p=0.842 Thrombocytopenia 23.2 vs. 19.7,	NR	Alternating or sequential combinations failed to improve survival

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Conclusions
Dec 2002 to Apr 2006	chemotherapy were randomized to group A or B.	Arm B: PE 4 cycles, followed by topotecan for 4 cycles	186	1 yr OS 36.5% vs. 43.8% (p=ns)	p=0.421 Nausea/vomiting 2.2 vs. 2.7, p=nr		
Ignatiadis et al. 2005 [34] Phase III Greece June 2000 to October 2003	284 chemo-naïve pts between 18-75 yrs old with a WHO PS of 0-2 were randomized	Sequential: PE (75 mg/m^2 D1; 100 mg/m^2 D1-3), 4 cycles of topotecan after (1.5 mg/m^2 D1-5). Repeated every 3 weeks	142	Sequential vs. Alternating: Median = 10.2 (95% CI 8.7-11.7) vs. 9.5 (95% CI 7.9-11.1), p=0.767 1 yr survival= 35.1% vs. 34.4%	Grade 4, Sequential vs. Alternating Neutropenia 34% vs. 27%, Febrile Neutropenia 6% vs. 5% Anemia 1% vs. 2% Thrombocytopenia 11% vs. 11% no sig difference. Only sig difference was Grade 3 Asthenia 8% vs. 2%, p=0.028	NR	Both groups archived similar median survival times, which are not different from those reported on current standard chemo regimens.
		Alternating: PE (75 mg/m^2 D1; 100 mg/m^2 D1-3) on cycles 1,3,5,7 and topotecan 1.5 mg/m^2 D1-5 on cycles 2,4,6,8.	142				
Masutani et al. 2000 [35] Phase III Japan Jan 1995 to Dec 1998	76 pts with ECOG PS of 0 or 1, age ≤75 years, no prior chemo or/and RT were randomized	CAV/PE-W (500 mg/m^2; 30 mg/m^2; 1 mg/m^2 D1) alternating weekly with PE (50 mg/m^2 D1; 75 mg/m^2 D1,2) 8 courses total	22	CAV/PE-W vs. CAV/PE Median: 62.1 wks (47.9-98.4) vs. 43.9 wks (35.3-54.6) log-rank difference, p=0.009	CAV/PE-W vs. CAV/PE Grade 3-4 thrombocytopenia 23.7% vs. 26.3%	NR	The weekly regimen showed improvements in survival time.
		CAV/PE (800 mg/m^2; 50 mg/m^2; 1.4mg/m^2 D1), alternating 3-week intervals with PE (100 mg/m^2 D1; 100 mg/m^2 D1,2,3) 4 courses total	19				
Schaefer et al. 2003 [36] Phase II US Nov 1994 to Feb 1998	40 pts with ECOG PS of 0-2, no previous chemo/RT; 20 additional pts were assigned to daily treatment scheduled after continuous scheduled closed due to insufficient activity.	Daily: 1.5 mg/m^2 topotecan D1 through 5, every 3 wks	40	Daily vs. Continuous: OS 18 (95% CI 11.8-20.1) vs. 12.5 mths (95% CI 5.8-19.2), p=nr Estimated K-M survival rates (%): 6 mths: 85 (95% CI 0.76-0.95) vs. 65 (95% CI 0.50-0.85) 12 mths: 63 (95% CI 0.51-0.76) vs. 55 (95% CI 0.39-0.77)	Grade 4, daily vs. continuous Leukopenia 27.5% vs. 15% Neutropenia 80% vs. 65% Thrombocytopenia 12.5% vs. 30%	NR	Topotecan is an active agent in SCLC when administered daily for 5 sequential days/3 wks. The 72 hr continuous infusion failed to demonstrate sufficient activity.
		Continuous: 1.3 mg/m^2 daily of topotecan over 72 hrs every 4 weeks	20				
Sculier et al. 2001 [37] Phase III Europe Apr 1993 t0	243 pts with no prior RT/chemo/ surgery and a Karnofsky PS of at least 60 were randomized to	Arm A: Standard Arm: administration every 3 weeks	78	Median: 286 days (233-349) 2yr OS: 5% (0-11%)	Grade 3/4 (A vs. B vs. C), % Leukopenia: 85 vs. 84 vs. 93, p=0.16 Thrombocytopenia: 16 vs. 45 vs. 22, p<0.001	NR	Results do not support the practice of chemo acceleration via the support by hematological
		Arm B: Accelerated Arm: administration every 2 weeks with GM-CSF support	78	Median: 264 days (220-308) 2yr OS: 6% (0-12%)			

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Conclusions
Apr 2000	receive 6 courses of EVI (epirubicin 90 mg/ vindesine 3 mg/ ifosfamide 5 g) given on D1 according to 3 different schedules	Arm C: administration every 2 weeks with oral antibiotic support (cotrimoxazole)	77	Median: 264 (223-305) 2yr OS: 6% (0-12%)	Nausea/vomiting: 9 vs. 10 vs. 14, p=0.63 Infections: 18 vs. 22 vs. 14, p = 0.43		growth factors in ES.
Sekine et al. 2003 [38] Phase II Japan Aug 1999 to Oct 2002	60 pts with no prior treatment; ECOG PS 0-2; age 20-70yrs; life expectancy >3 mths were randomized. G-CSF support was provided in both arms.	Arm A: Cisplatin (25 mg/m^2 D1) at 1 wk intervals for 9 wks + irinotecan (90 mg/m^2 D1 on wks 1,3,5,7,9) + etoposide (60 mg/m^2 D1-3 of weeks 2,4,6,8)	30	A vs. B: median: 8.9 mths vs. 12.9 mths 1 OS: 40% vs. 57% p=nr	Grade 3-4 (%): Leukocytopenia: 50% vs. 53% Neutropenia: 57% vs. 87% Anemia: 57% vs. 47% Thrombocytopenia: 27% vs. 10%	NR	Suggests that the cisplatin-irinotecan-etoposide combinations in both schedules have significant activity with acceptable toxicity.
		Arm B: Cisplatin (60 mg/m^2 D1) + irinotecan (60 mg/m^2 D1,8, and 15) + etoposide (50 mg/m^2 D1-3). Repeated every 4 weeks for a 4 cycles.	30				
Ueoka et al. 1998 [39] Phase unknown Japan April 1988 to October 1992	143 pts aged ≤75; ECOG PS 0-2; no prior chemo, RT, or surgery were randomized	Hybrid chemo: CAV (700 mg; 30 mg; 1.4 mg D1) and PE (60 mg; 100 mg D8). Repeated every 4 wks for up to 6 cycles	34	Hybrid vs. Sequential: Median: 9.7 mths (7.6-11.8) vs. 12.2 mths (10.8-13.6) 3yr OS: 4.6% vs. 3.5% no significant difference between groups, log rank p=0.81	NR	NR	Trial failed to demonstrate an advantage of one regimen over another.
		Sequential: CAV given twice between D1 and 8 at same dose as hybrid, repeated every 4 wks for initial 3 cycles. PE D1 and 8, repeated every 4 wks for 3 cycles.	32				
Veslemes et al. 1998 [40] Phase unknown Greece Years NR	70 pts aged ≤76 years, ECOG PS ≤3, and no prior chemo. Undergoing PE (80 mg D1; 120 mg D1-3).	Arm A: 4 cycles every 3 weeks	24	A vs. B: Median 6.5 months (4-16.5) vs. 9 months (95% CI 5-16), p=0.09	NR	NR	Trend in favor of 6 course therapy for ES pts.
		Arm B: 6 cycles every 3 weeks	22				
Xiao et al. 2015 [41] schedule China January 2011 to November	93 pts were randomized ECOG 0-2; assessable disease	IP (60 mg/m^2 D1, 8, 15; 75 mg/m^2 D1) every 4 weeks, followed by PE when tumour progressed	48	IP vs. PE: Median: 15.4 (95% CI 13.9-16.9) vs. 15.7 (95% CI 14.0-17.5), p=0.483	Grade 3,4 (frequency of events), IP vs. EP Anemia 2 vs. 5, p=0.249 Neutropenia 11 vs. 23, p=0.015 Thrombocytopenia 9 vs. 7, p=0.316 Diarrhea 10 vs. 2, p=0.012	NR	Short- and long-term effects are similar for the 2 groups, toxicity in the IP group was less.
		PE (75 mg/^{2} D1/100 mg/m^2 D1-3), followed by IP when tumour progressed	45				

Author, location, enrolment	Number of patients and characteristics	Arms or comparisons	Number pts analyzed	Overall Survival	Toxicity	Quality of Life	Conclusions
2013							

Abbreviations: CAV/EP = cyclophosphamide, doxorubicin, vincristine/etoposide cisplatin; CAV/EP-W = weekly alternating cyclophosphamide, doxorubicin, vincristine/etoposide cisplatin; CE = carboplatin/etoposide; chemo = chemotherapy; CI = confidence interval; D = day; ECOG = Eastern Cooperative Oncology Group; ES = extensive stage; fx = fraction; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte macrophage colony-stimulating factor; HR = hazard ratio; K-M = Kaplan–Meier; LS = limited-stage; mths = months; NR = not reported; ns = not significant; OS = overall survival; PE = cisplatin/etoposide; PS = performance status; pts = patients; RT = radiotherapy; SCLC = small cell lung cancer; WHO = World Health Organization

Table 4-21. Quality of evidence for studies selected for inclusion for LS SCLC and ES SCLC patients comparing optimal dose and schedule of chemotherapy.

Quality assessment								Quality	Importance
Study	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
LS: Overall Survival									
Leyvraz 2008 [14]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Scullier 2008 [15]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
LS: Toxicity									
Scullier 2008 [15]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	MPORTANT
ES (Dose): Overall Survival									
Baka 2010[33]	1	RCT	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ HIGH	CRITICAL
9 Studies[2] [32-41]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	CRITICAL
ES: Toxicity									
7 Studies[2] [32-34,36-38,41]	1	RCT	not serious	not serious	not serious	serious [1]	none	⊕⊕⊕◯ MODERATE	IMPORTANT

Abbreviations: ES = extensive-state; LS = limited-stage; RCT = randomized controlled trial; SCLC = small cell lung cancer

1. Number of events is lower and only one study
2. Aggregate scores of the studies were not possible as they reported on different doses and schedules. Quality of evidence of individual study was conducted.

DISCUSSION

As the leading cause of cancer-related deaths in Canada, lung cancer is a significant concern [54]. Approximately 10% to 15% of patients with lung cancer will be determined to have SCLC, the most aggressive of all types of lung cancer. At presentation, approximately 70% to 75% of patients will have ES SCLC, whereas the remaining 25% to 30% will have LS SCLC [54].

Chemotherapy is the most common treatment for SCLC due to its aggressive nature and early metastatic spread. Platinum-based chemotherapy is the standard of care for first-line therapy for LS SCLC and ES SCLC. The most commonly used platinum agents are cisplatin and carboplatin, which are often combined with a non-platinum agent, such as etoposide. When platinum-etoposide was compared with another platinum, non-platinum, platinum-etoposide with another agent, and platinum-etoposide with a targeted agent in patients with LS SCLC, it was found that the combination of cisplatin-etoposide had the greatest overall survival with the least adverse effects. This suggests that platinum-etoposide in combination with thoracic radiotherapy should remain the standard therapy for LS SCLC.

In patients with ES SCLC, platinum-etoposide remained the most effective treatment when compared with non-platinum, adding another agent to platinum-etoposide, or adding a targeted agent to platinum-etoposide. Recently, the combination of platinum-irinotecan has been of debate when compared with cisplatin-etoposide. In our meta-analysis of seven trials, induction chemotherapy with platinum-irinotecan resulted in longer overall survival compared with cisplatin-etoposide. Based on an a priori suspicion from the evidence of previous studies that the Japanese population may respond differently to irinotecan [28], a sensitivity analysis was conducted by removing the Noda et al. [21] trial. In this analysis, platinum-irinotecan still demonstrated a significant benefit for overall survival. Based on these findings, platinum-irinotecan should be considered as an option for patients with ES SCLC. Whether the benefit is greater in Asian subpopulations cannot be determined at this time. The small survival benefit of irinotecan and lower myelosuppression should be balanced against the greater incidences of diarrhea.

The use of chemotherapy and thoracic radiation therapy reflects the current standard of care for patients with LS SCLC [55,56]. In the current review, we investigated the addition of thoracic radiotherapy to chemotherapy for patients with ES SCLC. The addition of thoracic radiotherapy was shown to have a significant improvement in median overall survival in one trial; however, this was a smaller trial conducted more than 15 years ago and the thoracic radiotherapy involved higher doses and larger volumes than is typically used in North America [16]. Recently, a phase III trial reported that the addition of thoracic radiotherapy showed a trend to improving the primary endpoint of one-year overall survival, but did not reach statistical significance [19]. The secondary endpoints of 18-month and two-year overall survival did reach statistical significance [19]. Another recently reported randomized phase II trial did not show a difference in overall survival, although this trial also included thoracic radiotherapy to oligometastatic sites in addition to thoracic radiotherapy [17]. These data would suggest that the addition of thoracic radiotherapy to chemotherapy in ES SCLC should be considered on a case-by-case basis (e.g., low-volume extra-thoracic disease with residual intra-thoracic disease or high-volume pre-treatment disease), but cannot be considered to be the standard of care.

The administration of thoracic radiotherapy and the optimal timing, dosing and schedules has been of interest in many studies. Regarding the optimal timing of radiotherapy (early vs. late), the recent literature search revealed conflicting evidence and no new evidence for an optimal schedule (concurrent vs. sequential) for patients with LS SCLC. It was the consensus of the Working Group members that for pragmatic reasons that thoracic radiotherapy should be started as early as feasible and administered concurrently (e.g., early

consultation of radiation oncology). While an optimal dose of thoracic radiotherapy has not yet been established, trials that demonstrated a superior overall survival have generally used a total dose of at least 40 Gy in 15 fractions given daily over three weeks or 45 Gy in 30 fractions given twice per day (or a biologically equivalent dose). In patients with ES SCLC, there is currently no evidence as to the optimal timing, dosing, and schedule of thoracic radiotherapy.

CONCLUSIONS

In non-resected patients with LS SCLC (stage I, II, and III), there is evidence to suggest that cisplatin-etoposide in combination with thoracic radiotherapy should remain the standard therapy. There is insufficient evidence to recommend an optimal timing of radiotherapy (early vs. late) and optimal schedule (concurrent vs. sequential). Based on the consensus of the Working Group members, thoracic radiotherapy should be started as early as feasible and concurrently. Furthermore, there was insufficient evidence to conclude an optimal dose of thoracic radiotherapy; however, it is suggested that a total dose of at least 40 Gy in 15 fractions over three weeks (or a biologically equivalent dose) be used.

In non-resected patients with ES SCLC (stage IV), there is currently insufficient evidence to recommend the addition of thoracic radiotherapy to standard combination chemotherapy as the standard practice. The addition of thoracic radiotherapy could, however, be considered on a case-by-case basis. There was insufficient evidence to recommend optimal timing, schedule, or dose of thoracic radiotherapy. The most commonly used induction chemotherapy is platinum-etoposide; however, based on new evidence, platinum-irinotecan has been added as an option.

Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-Line Chemotherapy

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 26 members of the GDG Expert Panel, 21 (81%) members voted in December 2016 and January 2017. Of those that voted, 21 (100%) approved the document. The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. A request was made to clarify that there is no meaningful difference in the effectiveness of either cisplatin or carboplatin for the ES setting.	We have reworded the recommendation to "platinum-agent plus etoposide" relating to ES disease.
2. Dose fractionation: a. Based on the Faivre-Finn et al. and CONVERT trial results, should there also be a mention of 60-66 Gy/30-33 fraction once daily regimens as an acceptable schedule? b. "The best outcomes in terms of overall survival have been observed in trials using at least 40 Gy in 15 fractions once daily or 45 Gy in 30 fractions twice daily". Do we have a reference for the 40.5 Gy/15 fractions commonly used in Canada? The closest I see is the Norwegian 42 Gy/15 fractions (Gronberg).	The 40 Gy/15 fractions and recommendation for early vs. late come from the Murray et al. trial, which was in the original document [13]. This trial suggested that 66 Gy/33 fractions may be an acceptable alternative since the results did not show a difference. That is why the Working Group purposely left the wording as <u>at least</u> 40 Gy/15 fractions to cover higher doses such as 42.5 Gy/15 fractions and 66 Gy/33 fractions. The Working Group decided not to change the recommendation, but to underline the words, "at least", in the recommendation.
3. Qualifying statement ***"The total dose of etoposide per cycle of chemotherapy should be administered in divided doses given daily over <u>three to five</u> days."*** Although I am aware that some centres may give etoposide over five days, most give etoposide over three days. Also, Maksymiuk et al. do not refer to a five-day schedule (either bolus or three-day). None of the regimens mentioned later on in the document refer to a five-day schedule as well (sorry if I am missing something since	The five-day schedule has been removed.

this is purely a Med Onc issue).	

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document from November 2016 to January 2017. Two RAP reviewers approved the document in December 2016. One RAP reviewer did not approve the document in January 2017, but after extensive revisions that were summarized in Table 5-2, the RAP reviewer approved the document in April 2017.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
1. Start with an objectives statement and simplify the guideline history section.	We have moved the guideline objectives to the beginning of the document and have added a brief sentence on the guideline history.
2. Suggest reordering the recommendations such that you have a bundle focused on LS and then the bundle that focus on ES.	We have reordered the recommendations according to disease stage to help improve readability and utility.
3. Suggest deleting Appendix 5 of studies excluded where contemporary methods of standard of care were not used and add as an exclusion criteria	We have added it as an exclusion criterion and have deleted Appendix 5.
4. Consider removing abstract data as many studies were included and will add space and make the document less distracting	We have decided to keep the abstract data as the decision to not include is based after the fact and is less methodologically sound.
5. Consider adding the levels of evidence to the recommendations to highlight that many of the recommendations (or their qualifying statements) are based on expert opinion/consensus rather than data.	The quality of the evidence, and the risks and benefits of each recommendation is fully described in Section 2.
6. Suggest adding at the end of sentence in the Recommendation 5 qualifying statement "in patients treated with irinotecan" to help readability of recommendation.	We have made this suggestion to help readability of the qualifying statement.
7. For the recommendation regarding radiotherapy in patients with ES SCLC, the review of evidence is confusing. You mention one trial that showed improved survival and three trials that did not. Why are you saying insufficient evidence here when you then provide exceptions – low-volume extra-thoracic and high-volume pre-treatment? Why are these examples of exceptions? Are there others? Why do you not discuss these exceptions when reviewing the evidence? My concern is that these exceptions may be standard practice, but with no supporting evidence. It is fine if the panel wishes to support such exceptions, but more transparency is needed for reasons that supports these exceptions.	A rationale for including these subgroups of patients in the qualifying statement has been added.
8. The authors state that for pragmatic reasons, patients should start radiation as early as possible – despite lack of survival benefit and evidence of greater toxicity.	The justification was changed to "it was the consensus of the Working Group members that the current standard of care was to incorporate thoracic radiation early in the treatment of care. This is

Early radiation consult is viewed as helping to get early treatment. Please expand on 'pragmatic' comment. It would appear there is no evidence supporting early or delayed radiation.	reflected in the design of current clinical trials in LS SCLC that utilize radiation upfront with chemotherapy."
9. The authors support cisplatin-etoposide but they present evidence of a modest survival benefit with irinotecan. Previously signals of survival benefit from a single trial were enough to support the use of radiation – but evidence from a meta-analysis is not enough to support irinotecan – this does not appear logical. As well, only the side effect of diarrhea is mentioned and related to irinotecan. However, it would appear cisplatin-irinotecan causes more diarrhea, but less anemia, febrile neutropenia, etc. The consideration of evidence appears biased. It may be justified to negate irinotecan, but the current presentation of evidence to support the recommendations are not convincing.	The following comment was added at the end of the qualifying statement: "The clinical importance of this difference is unclear and irinotecan regimens are not currently funded by CCO for this indication."
10. Evidence from Asian trials is downplayed for some recommendations, but not others. The authors should be consistent, and expand on why data from Asian trials may not be generalizable to North American patients. While potentially legitimate, it would be good to expand on the rationale, and then, as mentioned, be consistent throughout the document with exclusion or inclusion of data from Asian trials.	The rationale for downplaying the evidence of the Japanese trial of irinotecan and cisplatin (Hoda) is the known pharmacogenomic differences between Japanese and North American populations. These considerations do not exist for radiation and there are no data suggesting different outcomes for radiation based on ethnicity.

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Four targeted peer reviewers from Ontario, Manitoba, British Columbia, and Alberta who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three agreed to be the reviewers (Appendix 1) and three responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	0	3
2. Rate the guideline presentation.	0	0	1	1	1

3. Rate the guideline recommendations.	0	0	0	3	0
4. Rate the completeness of reporting.	0	0	0	2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	2	1
6. Rate the overall quality of the guideline report.	0	0	0	1	2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	0	1	2
8. I would recommend this guideline for use in practice.	0	0	0	1	2
9. What are the barriers or enablers to the implementation of this guideline report?	• Lack of funding for irinotecan would make it difficult to use. • Although the document is well-organized, it is quite long and finding the relevant information can be cumbersome.				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. Although it is recommended to use TNM staging rather than limited and extensive, the way it is written here is confusing in terms of the appropriateness of the recommendations. I think this is mostly due to the use of the older staging (limited versus extensive) for the studies upon which the evidence is based. But included in the LS (stage I, II, and III) would be patients (primarily in stage III) that would clearly not be candidates for chemotherapy-radiation therapy. There should be some discussion of this.	Patients with stage III SCLC represent the majority of LS SCLC and are routinely treated with chemotherapy-radiation therapy, although some patients with stage III disease may have radiation fields that are too large to be considered safe. The following was added to the Target Population to increase clarity, "In keeping with recommendations from the International Association for the Study of Lung Cancer and Cancer Care Ontario, we have transitioned to the use of TNM staging rather than the Veterans Affairs staging of limited versus extensive stage. The target population for this guideline are adult patients with non-resected LS (stage I, II, and III) and ES (stage IV) SCLC who can safely receive definitive radiation."
2. I found the section on platinum-etoposide versus platinum-irinotecan difficult to follow. The "meta-analysis" was done on all trials and then excluding the Japanese trial by Noda et al. and again excluding Asian patients. There appear to me to be sufficient patients in the "Western" studies to do a meta-analysis. Why not just present that? While the p-value was significant for overall survival in favour of irinotecan when excluding the Noda et al. trial, the HR was 0.88. While statistically significant this is not really clinically relevant based on ASCO recommendations. I think this should be stated.	We have added that removing the trial by Noda et al. eliminated statistical heterogeneity. The second analysis was performed to examine non-Asian trials alone. It is still appropriate to include all trials in the initial meta-analysis. The point about the difference for irinotecan not being clinically important is the reason we are not recommending this as the preferred treatment, but it is still an alternative to platinum and etoposide. We mention this in the recommendations section and guideline section.
3. It would have been nice to see a discussion/recommendation addressing cisplatin versus carboplatin combined with etoposide in	There is a lack of data to demonstrate that one regimen is superior to another. Therefore, in ES SCLC, either regimen would be considered

the ES setting. I agree that cisplatin and carboplatin are equivalent in this setting, but the guideline does not present the evidence for the equivalence.	acceptable. Any trials that were conducted would have been included in previous PEBC guidelines.
4. I am not sure why the non-standard chemotherapies are included in the recommendation. To have a concise "Recommendation" section and then devote half a page to outlining "these agents are not routinely used as initial therapy…" seems at odds with the aim of a brief summary of what is recommended.	To keep Section 1 brief, the non-standard chemotherapy regimens have been removed, but have been retained in Section 2.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. One hundred fourteen medical professionals in the PEBC database from across Canada with an interest in lung cancer were contacted by email to inform them of the survey. Sixteen (14%) responses were received. Five stated that they were unavailable to review this guideline at the time. The results of the feedback survey from 11 healthcare professionals are summarized in Table 5-5.

Table 5-5. Responses to four items on the professional consultation survey.

	Number 11 (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	1(9)	10 (91)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	0	1(9)	10 (91)
3. I would recommend this guideline for use in practice.	0	0	0	1(9)	10 (91)
4. What are the barriers or enablers to the implementation of this guideline report?	• For institutions that are not currently following these recommendations, it may be difficult to change practice.				

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Name	Affiliation	Declarations of interest
Working Group		
Alexander Sun Radiation Oncologist	Princess Margaret Hospital Toronto, Ontario	None declared
Gail Darling Surgery	Princess Margaret Hospital Toronto, Ontario	None declared
Peter Ellis Medical Oncologist	Juravinski Cancer Centre Hamilton, Ontario	None declared
John Goffin Medical Oncologist	Juravinski Cancer Centre Hamilton, Ontario	Honorarium from Amgen, Boehringer Ingelheim and BMS
Kevin Ramchandar Radiation Oncologist	TBRHSC Regional Cancer Care Thunder Bay, Ontario	None declared
Yee Chung Ung Radiation Oncologist	Odette Cancer Centre Toronto, Ontario	None declared
Lisa Denise Durocher-Allen Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared
Lung Cancer Disease Site Group Expert Panel		
Jaro Kotalik Bioethicist	Lung Cancer Disease Site Group	None declared
Adrien Chan Medical Oncologist	Lung Cancer Disease Site Group	None declared
Susanna Cheng Medical Oncologist	Lung Cancer Disease Site Group	None declared
Ronald Feld Medical Oncologist	Lung Cancer Disease Site Group	Received at least $5,000 for research support from AstraZeneca, Helsin Therapeutics Inc., Molomed, Morphotek Inc., NCIC, Tesaro, Versatem, and Bristol Meyers Squibb.
Richard Gregg Medical Oncologist	Lung Cancer Disease Site Group	None declared
Swati Kulkarni Medical Oncologist	Lung Cancer Disease Site Group	None declared
Sara Kuruvilla Medical Oncologist	Lung Cancer Disease Site Group	None declared
Scott Laurie Medical Oncologist	Lung Cancer Disease Site Group	None declared
Natasha Leighl Medical Oncologist	Lung Cancer Disease Site Group	Received research support from Novartis in 2015 and Roche Canada in 2013
Andrew Robinson Medical Oncologist	Lung Cancer Disease Site Group	None declared

Mark Vincent Medical Oncologist	Lung Cancer Disease Site Group	None declared
Penelope Bradbury Medical Oncologist	Lung Cancer Disease Site Group	None declared
Medhat El-Mallah Radiation Oncologist	Lung Cancer Disease Site Group	None declared
Conrad Falkson Radiation Oncologist	Lung Cancer Disease Site Group	None declared
Robert MacRae Radiation Oncologist	Lung Cancer Disease Site Group	None declared
Andrew Pearce Radiation Oncologist	Lung Cancer Disease Site Group	None declared
Anand Swaminath Radiation Oncologist	Lung Cancer Disease Site Group	None declared
Mojgan Taremi Radiation Oncologist	Lung Cancer Disease Site Group	None declared
Edward Yu Radiation Oncologist	Lung Cancer Disease Site Group	None declared
Abdollah Behzadi Surgeon	Lung Cancer Disease Site Group	None declared
Donald Jones Surgeon	Lung Cancer Disease Site Group	None declared
Richard Malthaner Surgeon	Lung Cancer Disease Site Group	None declared
Donna Maziak Surgeon	Lung Cancer Disease Site Group	None declared
Julius Toth Surgeon	Lung Cancer Disease Site Group	None declared
Kazuhiro Yasufuku Surgeon	Lung Cancer Disease Site Group	Received an educational and research grant from the Olympus Corporation
Robert Zeldin Surgeon	Lung Cancer Disease Site Group	None declared
Report Approval Panel		
Melissa Brouwers Director	Program in Evidence-Based Care, Cancer Care Ontario, Hamilton, ON	None declared
Sebastien Hotte Medical Oncologist	Juravinski Cancer Centre, Hamilton, ON	None declared
Marko Simunovic Surgeon	Juravinski Cancer Centre, Hamilton, ON	None declared
Target Peer Reviewers		
Charles Butts Medical Oncologist	Department of Oncology University of Alberta Cross Cancer Institute Edmonton, AB	• Currently involved in a trial of nivolumab as maintenance therapy CheckMate 451; previously involved in a SCLC trial, "A randomized double-

		blind, placebo-controlled, phase 2 clinical trial of alisertib (MLN8237) in combination with paclitaxel versus placebo in combination with paclitaxel as second line therapy for SCLC" • Involved in developing Cancer Care Alberta lung guidelines
David Dawe Medical Oncologist	CancerCare Manitoba Winnipeg, MB	None declared
Devin Schellenberg Radiation Oncologist	Clinical Trial Director British Columbia Cancer Agency Fraser Valley Centre Surrey, BC	• Employed by the BC Cancer Agency • On the Organizational Board of the Canadian Lung Cancer Conference • Received an honorarium from Bayer Pharmaceuticals to speak about stereotactic radiation at a liver cancer conference

Appendix 2: Literature Search Strategy

1	Carcinoma, Non-Small-Cell Lung/ or NSCLC.ti. or (non adj small).ti. or nonsmall.ti. or non small cell lung cancer/
2	((small adj cell adj lung adj2 (tumo?r$ or adenocarcinoma$ or cancer$ or carcinoma$ or neoplasm$)) or SCLC or (oatcell or oat-cell or oat cell)).tw.
3	2 not 1
4	small cell lung carcinoma/ or small cell lung cancer/
5	3 or 4
6	exp Randomized Controlled Trial/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/ or Phase 3 Clinical Trial/ or Phase 4 Clinical Trial/ or ((exp Clinical Trial/ or Prospective Study/ or Prospective Studies/) and Random$.tw.) or exp Randomized Controlled Trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or exp "Randomized Controlled Trial (Topic)"/ or "Phase 3 Clinical Trial (Topic)"/ or "Phase 4 Clinical Trial (Topic)"/ or ((exp Clinical Trials as Topic/ or exp "Clinical Trial (Topic)"/) and random$.tw.) or Random Allocation/ or Randomization/ or Single-Blind Method/ or Double-Blind Method/ or Single Blind Procedure/ or Double Blind Procedure/ or Triple Blind Procedure/ or Placebos/ or Placebo/ or ((singl$ or doubl$ or tripl$) adj3 (blind$3 or mask$3 or dummy)).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (((phase II or phase 2 or clinic$) adj3 trial$) and random$).tw. or (placebo? or (allocat$ adj2 random$)).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
7	(exp evidence based practice/ or exp practice guideline/ or exp consensus development conference/ or guideline.pt. or practice parameter$.tw. or practice guideline$.mp. or (guideline: or recommend: or consensus or standards).ti. or (guideline: or recommend: or consensus or standards).kw.) not 6
8	(exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw. or (medline or med-line or pubmed or pub-med or embase or cochrane or cancerlit).ab.) not (6 or 7)
9	5 and 6
10	5 and 7
11	5 and 8
12	remove duplicates from 9
13	remove duplicates from 10
14	remove duplicates from 11
15	12 or 13 or 14

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Appendix 3: AMSTAR

Systematic review	' A priori' design	Duplicate study selection and data extraction	Comprehensive literature search	Status of publication as inclusion criterion	List of included and excluded studies	Characteristics of included studies provided	Scientific quality of included studies assessed	Scientific quality of included studies used appropriately in formulating	Methods used to combine findings of studies appropriate	Likelihood of publication bias assessed	Conflict of interest included
Amarasera et al. 2015 [93]	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N
Jett et al. 2013 [50]	Y	Y	Y	N	N	Y	Y	N	N	N	Y
Jiang et al. 2010 [94]	N	Y	Y	Y	Y	Y	N	N	Y	Y	N
Jiang et al. 2012 [95]	N	Y	Y	Y	Y	Y	N	N	Y	N	N
Lima et al. 2010 [96]	N	Y	Y	Y	Y	Y	N	N	Y	Y	N
Lu et al. 2014 [97]	N	Y	Y	N	N	N	N	N	Y	N	N
Mauguen et al. 2012 [98]	N	N	N/R	N	Y	Y	N	N	Y	N	Y
Palma et al. 2015 [99]	N	N	Y	N	N	Y	N	N	Y	Y	Y
Pijls-Johannesma et al. 2010 [100]	Y	Y	Y	N	Y	Y	Y	Y	Y	N	N
Rudin et al. 2015 [52]	Y	N	Y	N	N	Y	N	N	N	N	N
SIGN 2014 [45]	Y	Y	Y	N	N	N	Y	Y	N/R	N	N
Wang et al. 2012 [101]	N	Y	Y	Y	Y	Y	N	N	Y	N	N
Zhu et al. 2016 [102]	N	Y	Y	N	Y	Y	N	N	Y	N	N

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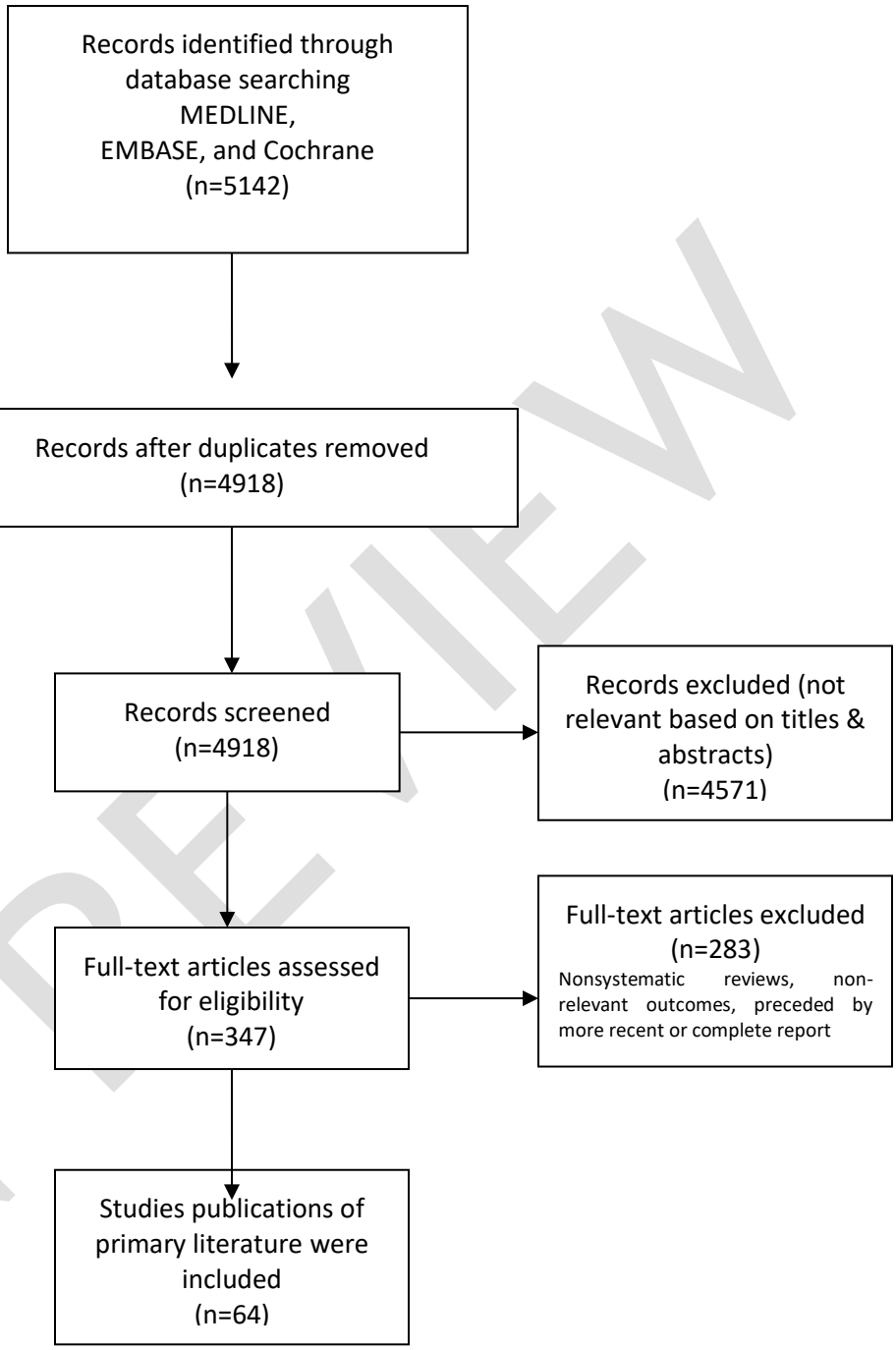
Appendix 4: PRISMA Flow Diagram



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Appendix 5. Methodological quality assessment of included studies.

Study	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawal described	Terminated early
Question 1						
Gore et al. 2015 [17] *abstract*	Yes	NR	To detect an improvement from 30% to 45% with a 34% hazard reduction (HR =0.66) under a 0.1 type 1 error (1 sided) and 80% power, 154 pts were required	NR	NR	Yes, closed the futility boundary for the primary endpoint
Jeremic et al. 1999 [16]	Yes	Partial	80% power, to detect an increase in CR rate to 50%, randomization of 106 pts (CR/CR and PR/CR) was planned.	NR	Yes	No
Narayan et al. 2015 [18] *abstract*	Yes	NR	NR	NR	NR	No
Slotman et al. 2015 [19]	Yes	Yes (no role in design, results, and writing of report).	Primary objective to compare OS at 1 year; a sample size of 483 pts was required to detect a 10% improvement in OS (HR 0-76) with 80% power at the 5% significance level (2 sided), allowing for a withdrawal rate of 5%.	NR	Yes	No
Question 2						
Spiro et al. 2006 [2]	NR	No	80% power (one-sided test) to detect an improvement of 10% (from 15% in late arm to 25% in the early arm), preplanned sample size of 320 patients.	NR	Yes	No
Sun 2013 [3]	NR	No	N = 196 in each group for non-inferiority margin of 20% for complete response rate. 80% power, α 0.05 (two-sided). With a 10% dropout rate, total planned N=218 pts	NR	Yes	No
Question 4						
Blackstock et al. 2005 [10]	Yes	NR	Expected a 122 pts per arm, only achieved 110 pts total, which approx. 70% power to detect differences and 80% to detect true differences of 25% (15% vs. 40%)	Yes	Yes	Yes, slow accrual
Faivre-Finn et al. 2016 [5] *abstract*	Yes	NR	NR	Yes	NR	No
Faivre-Finn et al. 2011 [11] *abstract*	NR	NR	NR	NR	Yes	No
Gronberg et al. 2016 [12]	Yes	Yes	To detect 30% improvement in 1 year from BID TRT, α=0.05 (2 sided), 75 pts/arm required. Expected 10% loss to f/u, aimed for 83 pts/arm	NR	Yes	No
Schild et al. 2004 [4]	Yes	Partial	80% power to detect 50% improvement in median survival (15 mth-22mths), preplanned sample size of 240	NR	Yes	No
Question 5						
Artal-Cortes et al. 2004 [63]	Yes, except >5% weight loss and Karnofsky index (more in epirubicin group)	NR	80% power to detect 2 yr difference, 2 sided log rank (α=0.05). Preplanned sample size was 420, with 5% expected losses.	Yes	Yes	No

Study	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawal described	Terminated early
Baka et al. 2008 [64]	Yes	NR	To detect a 1 yr OS difference of 20% (from 40-50%), 90% power (α=0.05 two sided), 280 pts required.	Yes	Yes	No
Eckardt et al. 2006 [23]	Yes	Partial	90% power α 0.05) to detect 8.6 mth med survival for PE arm and 11.3 mth med survival in TC arm, with recruitment time of 18 mths, max f/u of 30 mths and 8% drop out. Preplanned sample size of 380 per arm.	Yes	NR	No
Fink et al. 2012 [24]	Yes	No	Preplanned sample size of 350 per arm to detects median survival time of 8.5 mths for PE and 11.2 mths for TP arm (80% power for 2-sided log rank test, α=0.05) based on 29 mths accrual time and 12 mths f/u	Yes	Yes	Partial, one arm (Topotecan/Etoposide) was prematurely discontinued after unacceptable toxicity
Fujita et al. 2015 [65] *abstract*	NR	NR	NR	NR	Yes	NR
Han et al. 2008 [66]	Yes	Partial	Designed to detect increase in pts receiving maintenance chemo (α=0.05, β=0.02, one tailed). Preplanned sample size of 120 pts	NR	Yes	No
Hanna et al. 2006 [26]	Yes	No	Preplanned sample size of 300 pts (IP arm 200 EP arm 100) with 80% power to detect 30% improvement.	Yes	Yes	No
Hanna et al. 2002 [67]	Yes, except age	Partial	Preplanned accrual of 168 randomized pts for 80% power to detect a 50% increase in median survival, one sided level of 0.05	NR	Yes	No
Hermes et al. 2008 [27]	Yes, except slightly older patients (>70) in CE vs. IC arm, but difference was non-significant)	Yes	With a power of 80%, p=0.05 one-sided, the calculated number of pts was 200	NR	Yes	No
Jalal et al. 2015 [68] *abstract*	Yes	NR	NR	Yes	NR	Yes, due to negative effects in another trial
Kim et al. 2013 [22] *abstract*	NR	NR	NR	NR	NR	No
Kubota et al. 2014 [69]	Yes	Yes, but funding had no role in design, data collection/ analysis, interpretation or writing	Preplanned sample size was 250 pts and the expected number of events was 223, with a one sided α of 2.5% and at least 70% power to detect a difference between groups.	NR	Yes	No
Langer et al. 2014 [70]	Yes	Yes	Study had 55% power to detect a 33% increase in 1 yr OS with 146 evaluable subjects	Yes	Yes	No

Study	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawal described	Terminated early
Lara et al. 2009 [28]	Yes	No	90% power to detect a 33% increase in median survival in experimental arm, using one sided stratified log-rank test at level of 0.025, preplanned sample size of 310 pts per arm	Yes	Yes	No
Lee et al. 2009 [71]	Yes	Yes	Target sample size was 720 pts to detect a difference in 2 yr OS rate of 7% points, 85% power and 5% 2 sided	Yes	Yes	No
Lu et al. 2015 [72]	Yes	Yes	NR	Yes	Yes	No
Lyss et al. 2002 [73] *abstract*	Yes	Partial	Designed to differentiate 10% and 30% CR rate for each regimen. Preplanned sample size of 33 pts per arm. Type I and II error were 0.0042 and 0.094.	NR	yes	Partial, Arm 1 and 3 suspected due to rates of toxic death, Arm 2 no toxicity and led to early termination of accrual.
Mau-Soerensen et al. 2014 [25] *abstract*	Yes	NR	Sample size of 380 pts to detect an increase in 2 yr survival from 7.5-15% (α=0.05 ß=0.20)	NR	NR	Yes, slow accrual
Mavroudis 2001 [74]	Yes	No	5% sig level (one sided) and 80% power to detect an improvement, preplanned sample size of 460 pts (230 in each arm)	Yes	Yes	Yes, due to high toxicity (TEP arm)
McClay et al. 2005 [75]	Yes	NR	Designed with 80% power to detect a 40% increase in the median OS, α 0.05 (1 sided) preplanned sample size of 330 pts	NR	Yes	No
Niell 2005 [76]	Yes	Yes	A sample size of 580 pts was planned to detect a 30% improvement in median survival, one sided α=0.025, 80% power	NR	Yes	No
Noda et al. 2002 [21]	Yes	Partial	Preplanned sample sized of 230 pts, 3 yrs accrual, planned 80% power to detect improvement, α=0.05	NR	Yes	Yes, interim analysis showed benefit to one group over another.
O'Brien et al. 2011 [77]	Yes	No	Power of 80%, preplanned sample size was 27 pts per arm to detect an effect	NR	Yes	No
Oh et al. 2016 [78]	Yes, except median BMI index	Yes, but had no role in study design, data collection/ analysis, decision to publish/preparation of manuscript.	Estimated RR of 71% BP and 66% EP, with a non-inferiority margin of -15% at a power of 80%, one sided α at 0.05. Assuming a dropout rate of 1%, preplanned sample size was 150 pts	Yes	Yes	No
Pujol et al. 2001 [79]	Yes	Yes	To detect a 15% improved in 1 yrs OS in PCDE, a pre-planned sample size of 210 pts, ß =20%, α=0.05 (2 sided)	Yes	Yes	No
Pujol et al. 2015 [80]	Yes	Yes	Planned accrual was 75 pts, taking into account a ß risk of 20% and an α risk of 5%	Yes	Yes	No

Study	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawal described	Terminated early
Quoix et al.2005 [81]	Yes	NR	Planned for 100 pts to be enrolled and approx. 80 evaluated. As a phase II, not statistically powered but sufficient pts enrolled to enable judgement of risk/benefits	Yes	Yes	No
Ready et al. 2015 [82]	Yes	Partial	Inflated one-sided significance level of p=0.15, 89% power. Preplanned sample size of 80 pts.	NR	Yes	No
Rudin et al. 2008 [83]	Yes	Yes	Preplanned sample size of 55 pts (41 arm A 14 arm B). Size of arm A was chose that approx. 90% of power to differential 12 mth survival rate of 40-60%, $\alpha \leq 0.10$	Yes	Yes	No
Satouchi et al. 2014 [84]	Yes	Partial	Trial was designed to achieve at least 70% power, HR 1.31 (AP vs. IP), α 0.05, preplanned sample size of 282 pts	Yes	Yes	No
Schiller et al. 2001[85]	Yes	Partial	Based on one side log rank test with type 1 error of 2.5%, there was 90% power to detect 50% increase in median survival. Preplan accrual of 284 pts.	NR	Yes	No
Schmittel 2011 [29]	Yes	Yes	A total of 196 assessable pts needed to determine a different with α 0.05, taking into account 10% dropout, 216 pts had to be randomly assigned	NR	Yes	No
Sekine et al. 2014 [87]	Yes	Yes	At 5% 60 pts were needed for 90% power. Preplanned sample size of 130 pts, 65 in each arm	NR	Yes	Yes, terminated due to DMC recommendation.
Sekine et al. 2008[86]	Yes	Partial	Preplanned sample size of 55 pts in each arm for an accrual period of 24 mths	NR	Yes	No
Shi et al. 2015 [30]	Yes	Partial	NR	NR	NR	No
Socinski et al. 2009[88]	Yes	No	Assuming that HR = 1.0 and with a plan to enroll 1820 pts the analysis provided 83% power to reject null hypothesis.	Yes	Yes	Yes, due to futility after planned interim analysis
Spigel et al. 2011[89]	Yes	NR	Preplanned sample size of 100 pts. With approx. equal allocation, proving a 64% probability of observing one or more AE (2%) in BV group.	Yes	Yes	No
Sun et al. 2016 [90]	Yes	Yes	Power of 80%, α=0.05% two sided, a preplanned sample size of 300 pts to detect an effect	Yes	Yes	No
Sundstrom et al. 2002[91]	Yes, except there were more brain and lung metastases in CEV arm	NR	NR	Yes	Yes	No
Tamiya et al. 2015 *abstract[92]*	NR	NR	NR	NR	Yes	NR
Zatlouka et al. 2010 [31]	Yes	Yes	Power of 80%, α 0.05 to detect an increase in 1 year survival, preplanned pt sample of 404 (202 per arm)	Yes	Yes	No
Question 6						

Study	Balanced baseline characteristics	Industry funding	Statistical power and target sample size	ITT analysis	Withdrawal described	Terminated early
Baka et al. 2010[33]	Yes	NR	80% power (α=0.05 two sided) to detect a 4 mth difference in OS, preplanned sample size of 372 pts(186 on each arm)	No	Yes	No
Heigener et al. 2009[32]	NR	NR	Assuming median 9 mths (Arm A) and 15 mths (Arm B), with 5% significance level, preplanned sample of 136 per arm	NR	Yes	Yes, low accrual
Ignatiadis et al. 2005[34]	Yes (except brain metastasis)	NR	80% power (α=0.05) to detect a 4 mth superiority in OS in either arm, preplanned analysis 208 pts per arm. Interim analysis has 142 in each arm.	Yes	Yes	Interim analysis.
Leyvraz et al. 2008 [14]	Yes	Yes	Power of 90% (α=0.05), 3 yrs accrual, 1 yr f/u, study required 270 deaths for 360 pts accrued.	NR	Yes	Yes, slow accrual rate since 1997
Masutami et al., 2000[35]	Yes	NR	80% power (α=0.05, β=0.02) to detect an 80% prolongation of mean survival time (40-72 wks), preplanned sample 36 pts per arm.	NR	NR	No
Schaefer et al. 2003[36]	No	Partial	87% power (α=0.05) to detect a response of %30.	NR	Yes	Partial, continuous schedule closed due to insufficient activity
Sculier et al. 2008[15]	Yes	No	Expected in the standard arm a 2 yr survival rate of 10%, in order to have with experimental treatment, increased rate to 20%, estimated necessary number of events was 116 pts in each arm (α=0.05; β=20%; one side log rank test).	Yes	Yes	Yes, slow accrual rate since 1998
Sculier et al. 2001 [37]	Yes	NR	Designed to detect a 75% increase in median survival time, assumed 30 wks in control arm, in one of experimental arms (α=0.05, β=0.20), preplanned sample size of 78 pts in each arm and 195 deaths	Yes	Yes	No
Sekine et al. 2003[38]	Yes	Partial	Assuming response rates of poor and better arm of 70% and 85% and a correct selection probability of 90%, preplanned sample size of 30 in each arm.	NR	NR	No
Ueoka et al. 1998 [39]	Yes	No	NR	NR	Yes	Yes, interim analysis showed no clinically meaningful survival differences between groups.
Veslemes et al. 1998[40]	NR	NR	NR	NR	Yes	No
Xiao et al. 2015[41]	Yes	No	NR	NR	No	No

Abbreviations: AE = adverse events; AP = amrubicin/cisplatin; BID = twice daily; BMI = body mass index; CEV = cyclophosphamide, etoposide, vincristine; CR = complete response; DMC = Data Monitoring Committee ; EP = etoposide/cisplatin; f/u = follow-up; HR = hazard ratio; IP = irinotecan/cisplatin; ITT = intention-to-treat; mths = months; NR = not reported; OS = overall survival; PCDE = expoxorubicin/cyclophosphamide PE = cisplaten-etoposide; PR = partial response; pts = patients; RR = relative risk; TEP = paclitaxel, cisplatin, etoposide; TP = topotecan-etoposide; TRT = thoracic radiotherapy; yr = years

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Appendix 6. Risk of bias judgements of included studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants /personal	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Question 1						
Gore et al. 2015 [17] *abstract*	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Jeremic et al. 1999 [16]	Unclear	High	High	OS- Low Risk; Toxicity Low	Low	Low
Narayan et al. 2015 [18] *abstract*	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Slotman et al. 2015 [19]	Low	Low	High	OS- Low Risk; Toxicity Low	Low	Low
Question 2						
Spiro et al. 2006 [2]	Low	Unclear	Unclear	OS- Low; Toxicity Low	Low	Low
Sun et al. 2013 [3]	Low	Unclear	Unclear	OS- Low; Toxicity Low	Low	Low
Question 4						
Blackstock et al. 2005 [10]	Unclear	Unclear	Unclear	OS- Low; Toxicity Low	Low	Unclear
Faivre-Finn et al. 2016 [5] *abstract*	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Faivre-Finn et al. 2011 [11] *abstract*	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Gronberg et al. 2016 [12]	Low	Unclear	Unclear	OS- Low; Toxicity Low	Low	Low
Schild et al. 2004 [4]	Unclear	Unclear	Unclear	OS- Low; Toxicity Low	Low	Unclear
Question 5						
Alrtal-Cortes et al. 2004 [63]	Low	Low	Unclear	OS Low; Toxicity Low	Low	Unclear
Baka et al. 2008 [64]	Low	Low	Unclear	OS Low Toxicity Low	Low	Unclear
Eckardt et al. 2006 [23]	Low	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Fink et al. 2012 [24]	Unclear	Low	Unclear	OS Low; Toxicity Low	Low	Unclear
Fujita et al. 2015 [65] *abstract*	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Han et al. 2008 [66]	Low	Unclear	Unclear	OS low Toxicity Low	Low	Unclear
Hanna et al. 2006 [26]	Unclear	Low	Unclear	OS Low; Toxicity Low	Low	Unclear
Hanna et al. 2002 [67]	Low	Unclear	Unclear	OS Low Toxicity Low	Low	Unclear
Hermes et al. 2008 [27]	Low	Low	Unclear	OS Low; Toxicity Low; QoL Low	Low	Unclear
Jalal et al. 2015 [68] *abstract*	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Kim et al. 2013 [22] *abstract*	Unclear	Unclear	Unclear	OS Low Toxicity Unclear	Unclear	Unclear

Study	Random sequence generation	Allocation concealment	Blinding of participants /personal	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Kubota et al. 2014 [69]	Low	Low	Low	OS Low; Toxicity Low	Low	Unclear
Langer et al. 2014 [70]	Unclear	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Lara et al. 2009 [28]	Unclear	Low	Unclear	OS Low Toxicity Low	Low	Unclear
Lee et al. 2009 [71]	Low	Low	Low	OS Low	Low	Unclear
Lu et al. 2015 [72]	Unclear	Unclear	Unclear	OS Low; Toxicity Low QoL Low	Low	Unclear
Lyss et al. 2002 [73]	Unclear	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Mau-Soerensen et al. 2014 [25] *abstract*	Unclear	Unclear	Unclear	OS Low; Toxicity Unclear	Unclear	Unclear
Mavroudis 2001 [74]	Not clear	Low	Unclear	OS Low	Low	Unclear
McClay et al. 2005[75]	Unclear	Low	Unclear	OS Low Toxicity Low	Low	Unclear
Niell 2005 [76]	Low	Unclear	Unclear	OS Low Toxicity Low	Low	Unclear
Noda et al. 2002 [21]	Low	Unclear	Unclear	OS Low, Toxicity Low	Low	Unclear
O'Brien et al. 2011 [77]	Unclear	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Oh et al. 2016 [78]	Unclear	Unclear	Unclear	OS Low	Low	Unclear
Pujol et al. 2015 [80]	Low	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Quoix et al. 2005 [81]	Unclear	Unclear	Unclear	OS Low; Toxicity Low; QoL Low	Low	Unclear
Ready et al. [82]	Low	Unclear	Low	Low	Low	Unclear
Rudin et al. 2008 [83]	Unclear	Low	Unclear	OS Low; Toxicity Low	Low	Unclear
Satouchi et al. 2014 [84]	Unclear	Unclear	Unclear	OS Low; Toxicity Low, QoL Low	Low	Unclear
Schiller et al. 2001 [85]	Unclear	Unclear	Unclear	Low	Low	Unclear
Schmittel 2011 [29]	Low	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Sekine et al. 2014 [87]	Low	Not clear	Not clear	OS Low; Toxicity Low; QoL low	Low	Unclear
Sekine et al. 2008 [86]	Unclear	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Shi et al. 2015 [30]	Unclear	Unclear	Unclear	OS Low; Toxicity Low	Unclear	Unclear
Socinski et al. 2009 [88]	Low	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Spigel et al. 2011 [89]	Unclear	Unclear	Low	Low	Low	Unclear
Sun et al. 2016 [90]	Low	Low	Unclear	OS Low, Toxicity Low	Low	Unclear
Sundstrom et al. 2002 [91]	Low	Unclear	Unclear	OS Low	Low	Unclear
Tamiya et al. 2015 [92] *abstract*	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Zatlouka et al. 2010 [31]	Low	Unclear	Unclear	OS Low, Toxicity Low	Low	Unclear
Question 6						

Study	Random sequence generation	Allocation concealment	Blinding of participants /personal	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Baka et al. 2010 [33]	Unclear	Low	Unclear	OS Low; Toxicity Low	High ~50% of pts completed treatment as per protocol	High ~50% of pts completed treatment as per protocol
Heigener et al. 2009 [32]	Unclear	Unclear	Low	OS Low; Toxicity Low	Low	Unclear
Ignatiadis et al. 2005 [34]	Unclear	Low	Unclear	OS Low; Toxicity Low	Low	Low
Leyvraz et al. 2008 [14]	Low	Low	Low	OS Low; Toxicity Low	Low	Unclear
Masutani et al. 2000 [35]	Unclear	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Schaefer et al. 2003 [36]	Unclear	Unclear	Unclear	OS Low; Toxicity Low	Low	Low
Sculier et al. 2008 [15]	Low	Low	Not reported	OS Low; Toxicity Low	Low	Unclear
Sculier et al. 2001 [37]	Low	Low	Unclear	OS Low; Toxicity Low	Low	Low
Sekine et al. 2003 [38]	Unclear	Unclear	Unclear	OS Low; Toxicity Low	Low	Unclear
Ueoka et al. 1998 [39]	Unclear	Unclear	Unclear	OS Low	Low	Unclear
Veslemes et al. 1998 [40]	Low	High-envelopes-could possibly foresee assignments	Unclear	OS Low	Low	Unclear
Xiao et al. 2015 [41]	Unclear	Unclear	Unclear	OS Low; Toxicity Low	Unclear	Unclear

Abbreviations: OS = overall survival; pts = patients; QoL = quality of life

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Appendix 7: Ongoing trials (on October 31, 2016)

Protocol ID	Study details and Status
Combination Chemotherapy and Radiation Therapy in Treating Patients With Limited-Stage Small Cell Lung Cancer NCT00006012	Phase II trial to study the effectiveness of combination chemotherapy before, during, and after radiation therapy in treating patients who have LS SCLC (completed)
Amifostine, Chemotherapy, and Radiation Therapy in Treating Patients With Limited-Stage Small Cell Lung Cancer NCT00004176	Phase II trial to study the effectiveness of amifostine plus chemotherapy and radiation therapy in treating patients who have LS SCLC. (completed)
Radiation Therapy Regimens in Treating Patients With Limited-Stage Small Cell Lung Cancer Receiving Cisplatin and Etoposide NCT00632853	This randomized phase III trial is comparing different chest radiation therapy regimens to see how well they work in treating patients with limited-stage small cell lung cancer. (Recruiting)
Cisplatin, Etoposide, and Radiation Therapy in Treating Patients With Limited-Stage Small Cell Lung Cancer NCT00066222	This phase II trial is studying how well giving cisplatin and etoposide together with radiation therapy works in treating patients with limited-stage small cell lung cancer. (completed)
Clinical Randomized Study of Concurrent Chemo-radiotherapy vs. Radiotherapy Alone to Local-advanced Small Cell Lung Cancer NCT01745445	This trial aims to evaluate the efficacy and safety between radiotherapy alone and concurrent chemo-radiotherapy after 3-4 cycles of chemotherapy in LS-SCLC. (recruiting)
Study of Pembrolizumab and Chemotherapy With or Without Radiation in Small Cell Lung Cancer NCT02934503	This trial is to assess the efficacy of pembrolizumab added to concurrent chemotherapy with or without radiation therapy in patients with small cell lung cancer (recruiting)
Study of Pembrolizumab and Chemotherapy With or Without Radiation in Small Cell Lung Cancer NCT02934503	This trial is to assess the efficacy of pembrolizumab added to concurrent chemetherpay with or without radiation therapy in patients with small cell lung cancer (not yet open)
Hypofractionated Radiotherapy for Limited Stage Small Cell Lung Cancer NCT00907569	In this study, we propose to use a dose escalated hypofractionated regimen of chest radiotherapy for patients with LS-SCLC. (completed)
Comparable Study of Different Thoracic Radiotherapy Regimens for Extensive Stage Small Cell Lung Cancer NCT02675088	In this study, the investigators propose to give an increased dose of TRT to determine whether higher dose will improve 2-year OS, LC and progression-free survival (not yet open)
Radiation Therapy Plus Combination Chemotherapy In Treating Patients With Limited Stage Small Cell Lung Cancer NCT00003364	Randomized phase III trial to compare the effectiveness of radiation therapy given at different times along with combination chemotherapy in treating patients with limited stage small cell lung cancer. (completed)
Combination Chemotherapy Followed by Radiation Therapy in Patients With Small Cell Lung Cancer NCT00002822	Randomized phase III trial to compare the effect of two combination chemotherapy regimens followed by radiation therapy in treating patients with small cell lung cancer. (completed)
A Study Comparing Irinotecan and Cisplatin (IP) With Etoposide and Cisplatin (EP) Following EP/TRT for LD-SCLC NCT00144989	A Phase III Study Comparing Etoposide and Cisplatin (EP) With Irinotecan and Cisplatin (IP) Following EP Plus Concurrent Accelerated Hyperfractionated Thoracic Irradiation (EP/TRT) for Limited-Stage Small-Cell Lung Cancer (completed)
Hypofractionated vs. Conventionally Fractionated Concurrent CRT for LD-SCLC	The purpose of this study is to determine whether hypofractionated concurrent chemo-radiotherapy has the same efficiency as conventionally fractionated concurrent chemo-radiotherapy in Limited Disease Small Cell Lung Cancer. (recruiting)
Bevacizumab in Extensive Small Cell Lung Cancer NCT00930891	In this trial (IFCT-0802), standard chemotherapy (PCDE or PE) will be compared to experimental treatment (PCDE or PE + bevacizumab 7.5 mg/kg)

Protocol ID	Study details and Status
	for previously untreated SCLC patients. (completed)
A Study of Subjects With Previously Untreated Extensive-Stage Small-Cell Lung Cancer (SCLC) Treated With Platinum Plus Etoposide Chemotherapy With or Without Darbepoetin Alfa NCT00119613	The purpose of this study is to evaluate whether increasing or maintaining hemoglobin concentrations with darbepoetin alfa, when administered with platinum-containing chemotherapy in subjects with previously untreated extensive-stage small cell lung cancer (SCLC), increases survival. (completed)
Temozolomide as Maintenance Therapy Following Induction Chemotherapy in Extensive Stage Small Cell Lung Cancer NCT02772107	Temozolomide may delay progression in sequence with chemotherapy. This open-label, randomized,multicenter phase II trial was designed to evaluate the role of Temozolomide following 4 or 6 cycles of platinum-based first-line chemotherapy in patients with newly diagnosed estensive-stage SCLC. (recruiting)
Marimastat Following Chemotherapy in Treating Patients With Small Cell Lung CancerNCT00003011	Randomized phase III trial to compare the effectiveness of marimastat with a placebo following chemotherapy in treating patients who have small cell lung cancer. (completed)
A Study of Standard Treatment +/- Enoxaparin in Small Cell Lung Cancer (RASTEN) NCT00717938	The endpoint is to investigate if the addition of low molecular heparin - enoxaparin, will result in a significant increase of overall survival in patients with small cell lung cancer, receiving standard chemotherapy. (not recruiting)
Combination Chemotherapy in Treating Patients With Extensive-Stage Small Cell Lung Cancer NCT00041015	Randomized phase III trial to compare different chemotherapy regimens in treating patients who have extensive-stage small cell lung cancer. (completed)
Etoposide and Cisplatin or Carboplatin as First-Line Chemotherapy With or Without Pravastatin in Treating Patients With Small Cell Lung Cancer NCT00433498	This randomized phase III trial is studying etoposide and cisplatin or carboplatin to see how well they work when given as first-line chemotherapy together with pravastatin compared with first-line chemotherapy and a placebo in treating patients with small cell lung cancer. (completed)
Phase3 Study of Amrubicin With Cisplatin Versus Etoposide-cisplatin for Extensive Disease Small Cell Lung Cancer NCT00660504	The purpose of this study is to evaluate the efficacy and safety of amrubicin with cisplatin compared to etoposide-cisplatin in the first-line treatment in extensive disease small cell lung cancer
Randomized Study of Cisplatin-Etoposide Versus an Etoposide Regimen Without Cisplatin in Extensive Small-Cell Lung Cancer NCT00658580	The purpose of this study is to determine if a cisplatin-etoposide regimen improves survival in comparison to a regimen containing etoposide and without platinum derivative. (completed)
Carboplatin and Etoposide With or Without Thalidomide in Treating Patients With Limited-Stage or Extensive-Stage Small Cell Lung Cancer NCT00061919	This randomized phase III trial is studying carboplatin, etoposide, and thalidomide to see how well they work compared to carboplatin and etoposide in treating patients with limited- or extensive-stage small cell lung cancer.

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Appendix 8: Guideline Document History

GUIDELINE VERSIONS	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES and KEY CHANGES
	Search Dates	Data		
GL 7-13-1: The role of combination chemotherapy in the initial management of limited-stage small cell lung cancer [103,104]				
Original version – 7-13-1 March 2001	1985-2000	Full Report	Peer review publication. Web publication.	N.A.
Updated version 7-13-1 Dec 2003	2000-2003	New data added to original Full Report	Updated web publication.	Recommendations were modified in Jan 2003.
GL 7-13-3: The role of thoracic radiotherapy as an adjunct to standard chemotherapy in limited-stage small cell lung cancer [105]				
Original version 7-13-3	1990-1999	Full Report	Peer review publication. Web publication	N.A.
Updated version 7-13-3 January 2003	1999-2003	New data added to original full report	Updated web publication.	Recommendations were modified in Jan 2003.
GL 7-13: Initial management of small cell lung cancer (limited and extensive stage) and the role of thoracic radiotherapy and first line chemotherapy				
New guideline 7-13 October 2017	1996-2016	Merged limited stage data from 7-13-1 and 7-13-3 and added new data from 2002-2016 expanded scope of guideline to include extensive stage. Added new data from 1996-2016	Peer review publication. Web publication.	N.A.