Appendix E – Clinical evidence tables

Study	Title	Study characteristics	Risk of bias
Blackstock (2005)	Split-course versus continuous thoracic radiation therapy for limited-stage small-cell lung cancer: final report of a randomized phase III trial	Study type • Randomised controlled trial Study details • Study location USA • Study setting Multiple medical centres • Study dates Inclusion period: 1987 - 1992 • Duration of follow-up After the completion of treatment, patients were scheduled for evaluation every 2 months for 1 year, then every 4 months to a median of 14.7 months. For survival analysis minimum follow-up was 10.8 years for arm A and 12.8 years for arm B • Sources of funding Not mentioned. Inclusion criteria • Histologically proven small cell lung cancer • Acceptable radiotherapy target volume Exclusion criteria • ECOG performance status >3 • White blood cell count <4,000 /micro L • Platelet count <150,000 / micro L • Bilirubin concentration >1.5mg • Serum creatine concentration >1.5mg • aspartate aminotransferase concentration > 60 IU	Random sequence generation • Low risk of bias Randomised, non-stratified Allocation concealment • Unclear risk of bias Unlikely concealed Blinding of participants and personnel • High risk of bias non-blinded Blinding of outcome assessment • High risk of bias unlikely to have been blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate Unclear allocation concealment; non-blinded.

Study	Title	Study characteristics	Risk of bias
		• Age <18 years • When febrile neutropenia or severe nonhematologic toxicity occurred Sample characteristics • Sample size 114 people • Split between study groups 57 in each arm • Loss to follow-up 13 lost to follow-up or excluded following randomization • %female arm 1: 52% female arm 2: 26% female • Average age Arm 1: median age 63 (44-78) Arm 2: median age 60 (41-75) Interventions • Radiotherapy Cranial irradiation: All patients experiencing a complete response (CR) at the completion of treatment received prophylactic cranial irradiation (PCI) beginning 3 weeks after the last cycle of chemotherapy. • Chemotherapy All patients received same chemotherapy, which began on day 1 of therapy. Chemo was given over 6 cycles. Cycles 1, 2, and 5: given on weeks 0, 3 and 12 consisted of IV cisplatin 60 mg/m2 on day 1 after prehydration and IV etopside 120 mg/m2 on days 1, 2, and 3. Cycles 3, 4, and 6: Given on weeks 6, 9, and 15 and consisted of IV cyclophosphamide 750 mg/m2 on day 1, IV vincristine 2.0 mg on day 1, and doxorubicin 60 mg/m2 on day 1 • Continuous radiotherapy Given to arm 1: 50 Gy radiation (25 x 2.0gy) given 5 days	Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		per week concomitantly (day 1) with the first 2 cycles of the cisplatin/ etoposide chemotherapy. • Alternating radiotherapy Arm 2: 50 Gy (20 x 2.5gy) given concurrently on days 8-17 during the first two 21-day cycles of chemotherapy and on days 8 and 11 during the third 21-day cycle. Outcome measures • Survival • Adverse events (grade 3 or above)	
Bonner (1999)	Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma	Study type • Randomised controlled trial Study details • Study location USA • Study setting Multiple medical centres • Duration of follow-up Median: 39 (range 2 - 89) months Inclusion criteria • ECOG performance ECOG 0-2 • Other minimal pleural effusions • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • White blood cell count <3,500 cells/mm3 • Platelets <100,000 cells/mm3	Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias Unclear allocation concealment procedures Blinding of participants and personnel • Unclear risk of bias Unclear, likely not possible/done Blinding of outcome assessment • Unclear risk of bias Unclear, likely not possible/done Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias

Study	Title	Study characteristics	Risk of bias
		• History of another malignancy except a curatively resected non-melanoma skin cancer or in situ cervical cancer Unless 3-year period disease-free prior to study • Hemoglobin <9.5 g/dL • Creatine over 1.5 times upper limit of normal Sample characteristics • Sample size 324; 311 randomized • Split between study groups Once daily: 132 Twice daily: 130 • Loss to follow-up 62 lost to follow-up before receiving first three cycles of chemotherapy (due to death, progression, withdrawal and toxicity) • %female 42% female • Average age Average not reported Interventions • Radiotherapy Once daily: 48 Gy in 32 fractions, with a 2.5-week break after the initial 24 Gy Twice daily: 50.4Gy in 28 fractions • Chemotherapy All patients received three cycles of EP prior to any RT, each cycle consisting of three days EP. Two cycles were given concurrent with RT and one cycle was given post-RT Outcome measures • Survival Bonner 1999: 2 and 3-year survival rates Schild 2004: 5-	Other sources of bias • Low risk of bias Overall risk of bias • Moderate Lack of clarity regarding use of any blinding/allocation concealment procedures; likely not performed/not possible. Directness • Partially directly applicable Participants were only randomized after 3 cycles of chemotherapy, at which point radiotherapy began. In addition, treatment advancement relating to dosage and technique have been made since this study took place.

Study	Title	Study characteristics	Risk of bias
		year survival rates • Adverse events (grade 3 or above) Pneumonitis and eosphagitis	
Faivre-Finn (2017)	Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial	Study type • Randomised controlled trial Study details • Study location Belgium, Canada, France, Netherlands, Poland, Slovenia, Spain, UK. • Study setting 73 centres in 8 countries • Study dates 2008-2017 • Duration of follow-up Inclusion criteria • Age 18 years plus • ECOG performance status of 0-1 or; status of 2 due to disease-related symptoms (not co-morbidities) • Histologically proven small cell lung cancer Disease encompassed within a radical radiation portal • Acceptable radiotherapy target volume According to local radiotherapist Exclusion criteria • Other malignant pleural or pericardial effusions; > one adverse biochemical factor; Malignancy in past 5 years (except non-melanomatous skin or insitu cervix carcinoma) or	Random sequence generation • Low risk of bias Allocation concealment • Low risk of bias Allocation via phone by recruiting centre to Trails coordination unit Blinding of participants and personnel • Low risk of bias Not possible Blinding of outcome assessment • Low risk of bias Unlikely to have been blind Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate

Study	Title	Study characteristics	Risk of bias
		previous/concomitant illness or treatment that, in the opinion of the investigator, would interfere with the trial treatments or comparisons. • FEV/1s < 1 L or 40% of predicted value Sample characteristics • Sample size 547 randomly assigned • Split between study groups Once daily: 273 allocated, 240 received concurrent chemoradiotherapy, 270 were included in survival analysis Twice daily: 274 allocated, 249 received concurrent chemoradiotherapy, 273 were included in survival analysis • Loss to follow-up 4 lost to follow-up • %female Once daily: 45% Twice daily: 46% • Average age Once daily: 63 (34-81) Twice daily: 62 (29-84) • Smoking status Once daily: 39% current smoker, 60% ex-smoker, 2% never smoker. Twice daily: 34% current smoker, 64% ex-smoker, 1% never smoker. Interventions • Radiotherapy Once daily: 66 Gy (33 x 2Gy fractios) over 45 days given on 5 consecutive days. Twice daily: 45Gy in 30 x 1.5 Gy fractions with a minimum of 6h beween fractions, over 19 days, given on 5 consecutive days a week. • Chemotherapy	Non-blinded however allocation was likely concealed. Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		Outcome measures • Survival Overall and progression-free • Adverse events (grade 3 or above) Acute chemo toxicity (Nausea, vomiting, Mucositis, fatigue, motor and sensory neuropathy, infection, anaemia, febrile neutropenia, neutropenia, anorexia, other) Acute radiotherapy toxicity (Oesophagitis, pneumonitis) Late toxicity (Dermatitis, oesophagitis, oesophageal stricture or fistula, pulmonary fibrosis, pneumonitis, myelitis, other)	
Gronberg (2016)	Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer	Study type • Randomised controlled trial Study details • Study location Norway • Study setting 18 Hospitals in Norway • Study dates Inclusion period: 2005-2011 • Duration of follow-up PFS outcome: Median follow-up 59 months (range: 29-97), 34 patients were progression free at time of analysis (July, 2013). OS outcome: Median follow-up 81 months (range: 52-119), 34 patients were alive at time of the analysis (April, 2015). • Sources of funding "supported by the Central Norway Regional Health Authority (RHA), the Norwegian University of Science and Technology (NTNU) and the Norwegian Cancer Society."	Random sequence generation • Low risk of bias Randomised in blocks of 8 and stratified for the five Norwegian health care regions. Allocation concealment • Unclear risk of bias unclear whether allocation was concealed, unlikely to have been. Blinding of participants and personnel • Unclear risk of bias unclear blinding, unlikely to be blinded Blinding of outcome assessment • Unclear risk of bias unclear blinding, unlikely to be blinded Incomplete outcome data • Low risk of bias

Study	Title	Study characteristics	Risk of bias
		Inclusion criteria • Histologically proven small cell lung cancer measurable disease according to RECIST v1.0 • Other WHO performance status 0-2 • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • None reported • Pleural effusion unless one negative cytology • History of another malignancy except a curatively resected non-melanoma skin cancer or in situ cervical cancer • Previous treatment with systemic chemotherapy or radiation therapy • Platelets <100,000 /micro L • Age <18 years • White blood cell count <3,000 / micro L • Bilirubin >1.5 x ULN • Creatine >125 umol/l Sample characteristics • Sample size 171 enrolled, 157 analysed • Split between study groups Once daily: 89 randomized, 84 analysed Twice daily: 82 randomized, 73 analysed • Loss to follow-up 14 • %female 48% female • Average age	Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate Unlikely to have been blinded or have had allocation concealed. Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		Median age 63 years Interventions • Radiotherapy All participants received 3d-CRT 5x/week beginning 3-4 weeks after day 1 of first PE-course. Once daily hypofractionated: 42Gy (15 x 2.8gy) Twice daily conventional: 45Gy (30 x 1.5gy) • Chemotherapy All participants were to receive four courses of cisplatin (75 mg/m2 IV day 1) and etoposide (100 mg/m2 IV days 1-3 every 3 weeks). Outcome measures • Survival PFS and OS, 1-year • Adverse events (grade 3 or above) Pneumonitis, oesophagitis • QoL HR-QoL using EORTC quality of life questionnaire.	
Lebeau (1999)	A randomized clinical trial comparing concurrent and alternating thoracic irradiation for patients with limited small cell lung carcinoma. "Petites Cellules" Group	Study type • Randomised controlled trial Study details • Study location France • Study setting Multiple medical centres • Study dates Inclusion period 1988 - 1994 • Duration of follow-up	Random sequence generation • Low risk of bias randomized by a centralized telephone assignment procedure, stratified by center. Allocation concealment • Unclear risk of bias Unclear however possibly done as participants were randomized by a centralized telephone assignment procedure

Study	Title	Study characteristics	Risk of bias
		Median 66 months, minimum 19 months Inclusion criteria • ECOG performance 0-3 • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • Other history of neoplasm in last 5 years; renal, hepatic, or respiratory failure; or serious cardiac disease • Previous treatment with systemic chemotherapy or radiation therapy or curative surgery • Age >70 years Sample characteristics • Sample size 164; 156 randomized • Split between study groups Continuous: 82 Alternating: 74 • Loss to follow-up 36 patients originally included were either deemed ineligible or did not receive at least 80% of planned treatment. • Average age Mean 57.5 years Interventions • Chemotherapy Treatment consisted of IV combination of cyclophosphamide (1000 mg/m2 on Day 1), doxorubicin	Blinding of participants and personnel • High risk of bias non-blinded Blinding of outcome assessment • High risk of bias non-blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate Unclear allocation concealment; non-blinded Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		(45 mg/m2 on Day 1), and etoposide (150 mg/m2 on Days 1 and 2); doxorubicin was replaced by vindesine (3 mg/m2 on Day 1) for the second and third courses of chemotherapy to avoid the cardiotoxicity of the combination of doxorubicin and thoracic radiotherapy • Continuous radiotherapy 50Gy (20 x 2.5gy): 40Gy given in 16 fr over 28 days followed by 10gy in 4 fr over 7 days. Took place between days 30 - 64, covering 2nd and 3rd cycles of chemotherapy. • Alternating radiotherapy 55gy (22 x 2.5gy): first and second courses 20gy (8 x 2.5gy) over 12 days each, third course 15 gy (6x 2.5gy) over 10 days. Treatment was intercalated with 1-week rest periods before and after 2nd, 3rd, 4th and 5ht course of chemotherapy. Outcome measures • Survival	
Skarlos (2001)	Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG)	Study type • Randomised controlled trial Study details • Study location Greece • Study setting Multiple medical centres • Study dates Inclusion period 1993 - 1999 • Duration of follow-up A full re-evaluation included full blood count, liver and renal function tests, CT scan of the brain, thorax and abdomen	Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias Centrally randomized; unclear whether allocation was concealed Blinding of participants and personnel • High risk of bias Unlikely to have been blinded

Study	Title	Study characteristics	Risk of bias
		was performed every two cycles of chemotherapy. After completion of the treatment, the same re-evaluation was repeated every three months for the first year, every four months for the second year and every six months thereafter. The median follow-up was 35 months. • Sources of funding Not mentioned Inclusion criteria • Histologically proven small cell lung cancer Limited disease (confined to one hemithorax with involvement of mediastinal and/or ipsilateral supraclavicular lymphnodes) • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • Other Patients with pleural effusion; history of malignancy (except curatively resected non-melanoma skin cancer or in situ cervical cancer); those previously treated with systemic chemotherapy or radiotherapy • Pleural effusion • Contralateral supraclavicular lymph node involvement • ECOG performance status >2 • White blood cell count <3,500 cells/mm3 • Platelets <100,000 cells/mm3 • Hb <10 g/dl • Creatinine clearance <60 ml/min • History of another malignancy except a curatively resected non-melanoma skin cancer or in situ cervical cancer • Previous treatment with systemic chemotherapy or	Blinding of outcome assessment • High risk of bias Unlikely to have been blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • High risk of bias Greater drop-out rate in early-arm, partly due to toxicity. Overall risk of bias • High Unlikely to have been blinded, unclear allocation concealment procedures, higher attrition in early arm. Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		radiation therapy Sample characteristics • Sample size 81 people • Split between study groups Early radiotherapy + chemo = 42; Late radiotherapy + chemo = 39 • Loss to follow-up Early radiotherapy + chemo = 1; Late radiotherapy + chemo = 0 • %female Early radiotherapy + chemo = 7%; Late radiotherapy + chemo = 10% • Average age Median (range): Early radiotherapy + chemo = 61 years (40-76); Late radiotherapy + chemo = 60 years (37.5-76) Interventions • Radiotherapy Early: Received RT concurrently with first cycle of chemotherapy; Late: Received RT concurrently with fourth cycle All patients received 45Gy (30 x 1.5Gy, twice daily). • Chemotherapy "Chemotherapy consisted of carboplatin administered at an area under the curve (AUC) of six, I v by 1-hour infusion on day 1 immediately followed by etoposide at a dose of 100 mg/m2 i v by two-hour infusion for three consecutive days Treatment chemotherapy was repeated every three weeks up to a total of six cycles" • Early radiotherapy + chemo Early radiotherapy was done weeks 0 to 3. Chemotherapy consisted of carboplatin administered at an area under the curve (AUC) of six, IV by 1-hour infusion on day 1	

Study	Title	Study characteristics	Risk of bias
		immediately followed by etoposide at a dose of 100 mg/m2 IV by two-hour infusion for three consecutive days Treatment chemotherapy was repeated every three weeks up to a total of six cycles. Radiotherapy was given at a dose of 1.5 Gy per fraction twice daily up to a total of 45 Gy. Patients in this arm received radiotherapy concurrently with the first cycle of chemotherapy. An interval of at least four or, preferably, six hours between the two fractions was mandatory. Anterior- posterior fields were used The target volume for the first 30 Gy included the initial tumor area plus the bilateral medustinal and the ipsilateral hilar lymphnodes. The ipsilateral supraclavicular area was included in the radiation field, only in case of nodal involvement. The spinal cord was limited to 30 Gy The remaining 15 Gy were delivered to the primary tumor In group B, radiation fields were also determined by the initial tumor volume Dose correction was made for lung dishomogeneity. Prophylactic cranial irradiation (PCI) was delivered to patients who achieved a complete response. The whole brain was irradiated by using two lateral opposed fields to 20 Gy in five consecutive daily fractions of four Gy each. • Late radiotherapy + chemo Late radiotherapy was from weeks 9 to 12. Chemotherapy consisted of carboplatin administered at an area under the curve (AUC) of six, IV by 1-hour infusion on day 1 immediately followed by etoposide at a dose of 100 mg/m2 IV by two-hour infusion for three consecutive days. Treatment chemotherapy was repeated every three weeks up to a total of six cycles. Radiotherapy was given at a dose of 1.5 Gy per fraction twice daily up to a total of 45 Gy. Patients in this arm received radiotherapy concurrently with the fourth cycle of chemotherapy. An interval of at least four or, preferably, six hours between the two	

Study	Title	Study characteristics	Risk of bias
		fractions was mandatory. Anterior- posterior fields were used The target volume for the first 30 Gy included the initial tumor area plus the bilateral medustinal and the ipsilateral hilar lymphnodes. The ipsilateral supraclavicular area was included in the radiation field, only in case of nodal involvement. The spinal cord was limited to 30 Gy The remaining 15 Gy were delivered to the primary tumor In group B, radiation fields were also determined by the initial tumor volume Dose correction was made for lung dishomogeneity. Prophylactic cranial irradiation (PCI) was delivered to patients who achieved a complete response. The whole brain was irradiated by using two lateral opposed fields to 20 Gy in five consecutive daily fractions of four Gy each. Outcome measures • Survival overall and progression-free • Adverse events (grade 3 or above) Oesophagitis toxicity grade 3	
Spiro (2006)	Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis	Study type • Randomised controlled trial Study details • Study location UK • Study setting Multiple medical centres • Study dates Inclusion period: 1993 - 1999 • Duration of follow-up The median follow-up time for all patients was 63 months.	Random sequence generation • Low risk of bias Patients were randomly assigned using minimization, with stratification by center,ECOG performance status, sex, and whether or not they had undergone a CT brain scan. Allocation concealment • Unclear risk of bias unlikely to have been concealed

Study	Title	Study characteristics	Risk of bias
		• Sources of funding None reported Inclusion criteria • Histologically proven small cell lung cancer measurable/assessable and limited disease (within one hemithorax, mediastinum, or ipsilateral supraclavicular fossa) • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • Previous treatment with systemic chemotherapy or radiation therapy • Age >75 years • ECOG performance status >3 • White blood cell count <3,000 /micro L • Platelets <100,000 /micro L • Bilirubin >34.2 mmol/L • Creatinine clearance <50 ml/min • Disease could not be encompassed within the radiotherapy field • Condition that would exclude the use of thoracic radiotherapy Sample characteristics • Sample size 325 people • Split between study groups Early radiotherapy + chemo = 159; Late radiotherapy + chemo = 166 • Loss to follow-up Early radiotherapy + chemo = 1; Late radiotherapy +	Blinding of participants and personnel • High risk of bias non-blinded Blinding of outcome assessment • High risk of bias Non-blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • High risk of bias 83 participants did not finish all six courses of chemotherapy, with greater drop-out in early arm. In particular, toxicity and being deemed unfit were more likely to cause drop-out in the early arm. Overall risk of bias • High High attrition, differing between arms and toxicity-related. Non-blinded and allocation unlikely to have been concealed. Directness • Partially directly applicable Used a once-daily, very high dose-per-fraction regimen

Study	Title	Study characteristics	Risk of bias
		chemo = 2 • %female Early radiotherapy + chemo = 40%; Late radiotherapy + chemo = 43% • Average age Median (range): Early radiotherapy + chemo = 62 years (34-74); Late radiotherapy + chemo = 62 years (33-74) Interventions • Early radiotherapy + chemo Patients were randomly assigned to early thoracic radiotherapy administered concurrently with the first cycle of EP (week 3). The third cycle of chemotherapy (cyclophosphamide, doxorubicin, and vincristine) in the early radiotherapy arm was delayed for 1 week to allow patients to recover from the effects of radiotherapy and chemotherapy. All patients received the following chemotherapy administered intravenously: cyclophosphamide 1,000 mg/m2, doxorubicin 50 mg/m2, and vincristine 2mg total dose administered on day 1 of a 3-week cycle (cyclophosphamide, doxorubicin, and vincristine [CAV]), alternating with etoposide (100 mg/m2) and cisplatin (25 mg/m2) administered on days 1 to 3 (EP). A total of six cycles were intended, with each chemotherapy combination administered three times. Dose modification schedules were based on either the pretreatment or nadir neutrophils and platelets (whichever were the lowest), the pretreatment serum creatinine, or creatinine clearance and bilirubin. All drugs were reduced to 75% of the dose if the nadir neutrophil count was less than 0.2 X 109/L and/or the platelet count was less than 50 X 109/L or if the pretreatment neutrophil count was less than 2.0 X 109/L and/or the platelet count was less than 100 X 109/L. If the pretreatment neutrophil count was less	

Study	Title	Study characteristics	Risk of bias
		than 1.5 X 109/L and/or the platelet count was less than 75 X 109/L, the cycle would be delayed by 1 week or until neutrophils and platelets had recovered. If the serum creatinine was between the upper limit of normal (ULN) and less than 1.3 X ULN or creatinine clearance was 50 to 70 mL/min, the dose of cisplatin was reduced to 60%. If the serum creatinine was more than 1.3 X ULN or creatinine clearance was less than 50 mL/min, the cisplatin dose was omitted. Doxorubicin was reduced by 25% if the bilirubin level was between 20 and 25.9 TRT consisted of 40 Gy in 15 fractions over 3 weeks using cobalt-60 or a linear accelerator. The radiation began on day 1 of the first course of EP (ie, week 3) provided there was no evidence of progressive disease. The technique used was anterior and parallel-opposed fields with shielding of uninvolved lung. The thoracic spine was shielded to minimize the dose to the spinal cord to 35 Gy. The field size, which was based on the prechemotherapy tumour, was to be planned to encompass the primary tumor with a minimum 2 cm margin plus the entire mediastinum, with the supraclavicular lymph nodes if they were thought to be involved. Radiotherapy was continued regardless of the neutrophil count unless there was severe toxicity. Prophylactic cotrimoxazole (2 tablets bid) was administered from day 1 of each cycle of chemotherapy in which the patient received concomitant radiotherapy until the beginning of the next cycle prophylactic cranial irradiation. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was administered to responding patients who had a negative CT brain scan after completion of radiotherapy and all chemotherapy. Parallel opposing 20 X 17 cm fields were used, with a cobalt-60 or a linear accelerator. The whole brain was irradiated (with the inferior border following a line drawn to avoid the	

Study	Title	Study characteristics	Risk of bias
		eyes), including the temporal fossae and the intracranial portion of the cranial nerves. Treatment began on approximately day 8 of the third cycle of EP in the early radiotherapy group. • Late radiotherapy + chemo Patients were randomly assigned to late radiotherapy administered concurrently with the sixth cycle of chemotherapy (ie, third cycle of EP; week 15). All patients received the following chemotherapy administered intravenously: cyclophosphamide 1,000 mg/m2, doxorubicin 50 mg/m2, and vincristine 2mg total dose administered on day 1 of a 3-week cycle (cyclophosphamide, doxorubicin, and vincristine [CAV]), alternating with etoposide (100 mg/m2) and cisplatin (25 mg/m2) administered on days 1 to 3 (EP). A total of six cycles were intended, with each chemotherapy combination administered three times. Dose modification schedules were based on either the pretreatment or nadir neutrophils and platelets (whichever were the lowest), the pretreatment serum creatinine, or creatinine clearance and bilirubin. All drugs were reduced to 75% of the dose if the nadir neutrophil count was less than 0.2 X 109/L and/or the platelet count was less than 50 X 109/L or if the pretreatment neutrophil count was less than 2.0 X 109/L and/or the platelet count was less than 100 X 109/L. If the pretreatment neutrophil count was less than 1.5 X 109/L and/or the platelet count was less than 75 X 109/L, the cycle would be delayed by 1 week or until neutrophils and platelets had recovered. If the serum creatinine was between the upper limit of normal (ULN) and less than 1.3 X ULN or creatinine clearance was 50 to 70 mL/min, the dose of cisplatin was reduced to 60%. If the serum creatinine was more than 1.3 X ULN or creatinine clearance was less than 50 mL/min, the cisplatin dose was	

Study	Title	Study characteristics	Risk of bias
		omitted. Doxorubicin was reduced by 25% if the bilirubin level was between 20 and 25.9 TRT consisted of 40 Gy in 15 fractions over 3 weeks using cobalt-60 or a linear accelerator. The radiation began on day 1 of the third course of EP (i.e., week 15) provided there was no evidence of progressive disease. The technique used was anterior and parallel-opposed fields with shielding of uninvolved lung. The thoracic spine was shielded to minimize the dose to the spinal cord to 35 Gy. The field size, which was based on the prechemotherapy tumour, was to be planned to encompass the primary tumor with a minimum 2 cm margin plus the entire mediastinum, with the supraclavicular lymph nodes if they were thought to be involved. Radiotherapy was continued regardless of the neutrophil count unless there was severe toxicity. Prophylactic cotrimoxazole (2 tablets bid) was administered from day 1 of each cycle of chemotherapy in which the patient received concomitant radiotherapy until the beginning of the next cycle prophylactic cranial irradiation. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was administered to responding patients who had a negative CT brain scan after completion of radiotherapy and all chemotherapy. Parallel opposing 20 X 17 cm fields were used, with a cobalt-60 or a linear accelerator. The whole brain was irradiated (with the inferior border following a line drawn to avoid the eyes), including the temporal fossae and the intracranial portion of the cranial nerves. Treatment began on approximately 2 weeks after the end of radiotherapy in the late group. Outcome measures • Survival overall and progression-free	

Study	Title	Study characteristics	Risk of bias
		• Adverse events (grade 3 or above) aesophagitis	
Sun (2013)	Phase III trial of concurrent thoracic radiotherapy with either first- or third-cycle chemotherapy for limited-disease small-cell lung cancer.[Erratum appears in Ann Oncol. 2014 Aug;25(8):1672]	Study type • Randomised controlled trial Study details • Study location South Korea • Study setting Multiple medical centres in South Korea • Study dates Inclusion period: 2003- 2010 • Duration of follow-up Median 59.4 months • Sources of funding None reported Inclusion criteria • Histologically proven small cell lung cancer Limited disease (confined to one hemithorax, the mediastinum, and the bilateral supraclavicular fossae). • Other At least one measurable tumorous legion; adequate hematological, hepatic and renal function Exclusion criteria • Other Previous treatment with chemotherapy or radiation therapy • FEV/1s inadequate	Random sequence generation • Low risk of bias "randomly assigned in a 1:1 ratio into the early and late TRT arms. Treatment was assigned using block randomization with variable block sizes. At randomization, patients were stratified by center." Allocation concealment • Unclear risk of bias unclear whether allocation was concealed Blinding of participants and personnel • High risk of bias Unlikely to have been blinded Blinding of outcome assessment • High risk of bias Unlikely to have been blinded Incomplete outcome data • High risk of bias almost 20% of patients did not receive allocated radiotherapy and chemotherapy schedule. However, it is worth noting that this rate was similar between groups. Selective reporting • Low risk of bias

Study	Title	Study characteristics	Risk of bias
		Sample characteristics • Sample size 222 • Split between study groups Early: 113 (2 excluded following assignment) Late: 109 (one excluded following assignment) • Loss to follow-up 43 of originally assigned 222 participants were lost to follow-up/did not receive treatment. • %female 11% female • Average age Median age 60 years (39-75 years) Interventions • Early radiotherapy + chemo Participants received 4 cycles of chemotherapy every 21 days. Participants in this arm were assigned to receive radiotherapy with the first cycle of chemotherapy. Chemotherapy was administered every 3 weeks for four cycles. Etoposide (100 mg/m2 per day on days 1–3) and cisplatin (70 mg/m2 on day 1; EP) of each cycle were given by intravenous infusion. After the first cycle of chemotherapy, dose adjustments were allowed according to renal, hematologic, or other toxic effects. All radiotherapy was commenced using photons generated from linear accelerators following contrast-enhanced CT simulation and computerised treatment planning. The planning target volume encompassed the clinical target volume (CTV) with adequate margins in all directions (usually 1–1.5 cm). Three-dimensional conformal radiation therapy (3D-CRT) was planned in all patients, and dose constraints for lung were <20 Gy for MLD (mean lung dose) and 35% for V20. Pencil beam convolution algorithm	Other sources of bias • Low risk of bias Overall risk of bias • Moderate Unlikely that any blinding or allocation concealment was performed; high dropout rate. Directness • Partially directly applicable Used a once-daily, high dose-per-fraction regimen

Study	Title	Study characteristics	Risk of bias
		was used for dose calculation and lung tissue correction was applied. Total dose radiotherapy was 52.5 Gy with 2.1 Gy per fraction in once a day and five times a week for consecutive 5 weeks. All gross tumours were fully covered by prescribed dose and spinal cord dose was limited to 50 Gy. Radiotherapy was to begin on day 1 in this 'early' arm. Radiotherapy was to be continued, unless there was an uncontrollable severe toxic effect. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was administered to the patients who achieved complete response or very good partial response following the planned treatment course. • Late radiotherapy + chemo Participants received 4 cycles of chemotherapy every 21 days. Participants in this arm were assigned to receive radiotherapy with the third cycle of chemotherapy (at week 9). Chemotherapy was administered every 3 weeks for four cycles. Etoposide (100 mg/m2 per day on days 1–3) and cisplatin (70 mg/m2 on day 1; EP) of each cycle were given by intravenous infusion. After the first cycle of chemotherapy, dose adjustments were allowed according to renal, hematologic, or other toxic effects. All radiotherapy was commenced using photons generated from linear accelerators following contrast-enhanced CT simulation and computerised treatment planning. The planning target volume encompassed the clinical target volume (CTV) with adequate margins in all directions (usually 1–1.5 cm). Three-dimensional conformal radiation therapy (3D-CRT) was planned in all patients, and dose constraints for lung were <20 Gy for MLD (mean lung dose) and 35% for V20. Pencil beam convolution algorithm was used for dose calculation and lung tissue correction was applied. Total dose radiotherapy was 52.5 Gy with 2.1 Gy per fraction in once a day and five times a week for	

Study	Title	Study characteristics	Risk of bias
		consecutive 5 weeks. All gross tumours were fully covered by prescribed dose and spinal cord dose was limited to 50 Gy. Radiotherapy was to begin on the third cycle of EP chemotherapy in this arm. In this 'late' arm, the CTV modification reflecting tumour shrinkage following chemotherapy was done with reference to the postchemotherapy chest CT images. The initially involved mediastinal nodal stations, however, were to be included within the CTV even though a significant clinical response had occurred. Radiotherapy was to be continued, unless there was an uncontrollable severe toxic effect. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was administered to the patients who achieved complete response or very good partial response following the planned treatment course. Outcome measures • Survival Overall, progression-free • Adverse events (grade 3 or above) Toxic effects as according to National Cancer Institute Common Toxicity Criteria	
Takada (2002)	Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104	Study type • Randomised controlled trial Study details • Study location Japan • Study setting 16 medical centres/hospitals across Japan • Study dates Enrolment period: May 1991 to January 1995. Final	Random sequence generation • Low risk of bias Randomization was performed centrally using the minimization method of balancing institution and PS at the JCOG Data Center. Allocation concealment • Low risk of bias Performed centrally and therefore likely to have

Study	Title	Study characteristics	Risk of bias
		analysis was performed in August 2000 • Duration of follow-up Follow-up between 5 and 9 years • Sources of funding Supported in part by Grants-in-Aid for Cancer Research 2S-1, 5S-1, 8S-1, 11S-2, and 11S-4 and by the Second Term Comprehensive 10-Year Strategy for Cancer Control, all from the Ministry of Health, Labor, and Welfare. Inclusion criteria • ECOG performance 0-2 • Histologically proven small cell lung cancer • Other Adequate organ function • Limited disease (within one hemithorax, with or without mediastinal, supraclavicular or hilar lymph node involvement) Exclusion criteria • Other Arterial oxygen pressure <70 mmHg; stage I disease according to the tumour-node-metastasis staging method; symptomatic cardiac disease or history of MI in previous 3 months. • Pleural effusion • Age >75 years • Platelets <100,000 /micro L • White blood cell count <4,000 /micro L • Hemoglobin 11 g/dL or less • Creatine > 1.5 mg/dL • Serum AST and ALT levels over 2 x ULN • Serum bilirubin over 2.0 mg/dL	been concealed Blinding of participants and personnel • Unclear risk of bias Likely non-blinded Blinding of outcome assessment • Unclear risk of bias Likely non-blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Non-blinded however allocation was likely concealed and blinding is unlikely to affect primary outcome (Survival) Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		• 24-hour creatine clearance < 60 mL/min/m2 Sample characteristics • Sample size 231; 224 analysed • Split between study groups 114 early 114 late • Loss to follow-up 3 excluded post-randomisation; a further 9 did not have toxicity data. • %female Early: 20% female Late: 18% female • Average age Early: median age 64 (range 30-74) Late: median age 65 (range 39-74) Interventions • Chemotherapy Chemotherapy was given in a 28-day cycle in the concurrent arm and a 21-day cycle in the sequential arm. Chemotherapy consisted of cisplatin (80 mg/m2 IV) on day 1 and etoposide (100 mg/m2 IV) on days 1, 2, and 3. If leukocyte decreased to< 3,000/mm3 or the platelet count < 75,000/mm3 on the first day of next cycle, chemotherapy was withheld until the counts recovered. During cycles 3 and 4, the dose of etoposide was reduced to 75% of the initial dosage for patients who experienced grade 4 hematologic toxicity in the previous cycle. Study chemotherapy was terminated in patients with serum creatinine levels of 2.0 mg/dL or higher, serum bilirubin levels of 2.0 mg/dL or higher, or failure of the hepatic transaminase level to fall below 100 IU/L after 6 weeks of the prior cycle. • Early radiotherapy + chemo	

Study	Title	Study characteristics	Risk of bias
		Began on day-2 of first cycle. Administered twice-daily for 1.5Gy per fraction to a total of 45Gy in 3 weeks. After TRT, prophylactic whole-brain irradiation was administered to patients with a complete or near-complete response, to a dose of 24 Gy in 1.5-Gy fractions twice daily, 5 days per week. • Late radiotherapy + chemo Began on day-2 of fourth cycle. Administered twice-daily for 1.5Gy per fraction to a total of 45Gy in 3 weeks. After TRT, prophylactic whole-brain irradiation was administered to patients with a complete or near-complete response, to a dose of 24 Gy in 1.5-Gy fractions twice daily, 5 days per week. Outcome measures • Survival Overall survival • Adverse events (grade 3 or above) oesophagitis; Treatment-related death	
Turrisi (1999)	Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide	Study type • Randomised controlled trial Study details • Study location USA • Study setting Medical centre • Study dates Inclusion period: 1989-1992 • Duration of follow-up Median follow-up 8 years, 5 years minimum follow-up • Sources of funding	Random sequence generation • Low risk of bias "Randomized according to a permuted-block scheme, stratified according to Eastern Cooperative Oncology Group performance status (0 or 1 vs. 2), sex, and weight loss during the six months before entry (less than 5 percent of body weight vs. 5 percent or more)" Allocation concealment • Unclear risk of bias Unclear whether steps were taken to conceal

Study	Title	Study characteristics	Risk of bias
		Supported in part by Public Health Service grants (NCI, NIH and department of health and human services) Inclusion criteria • Histologically proven small cell lung cancer confined to one hemithorax, the ipsilateral supraclavicular fossa, or both. Exclusion criteria • Other pleural effusions found on chest films; contralateral hilar or supraclavicular adenopathy; Symptomatic cardiac disease or a myocardial infarction within the previous six months; Patients with prior cancer or prior treatment with either chemotherapy or radiotherapy Sample characteristics • Sample size 419 patients • Split between study groups Once daily: 206 Twice daily: 211 • Loss to follow-up 36 excluded from the analysis of eligible patients, 7 withdrew and never received therapy, and 29 were found to be ineligible • %female Once daily: 41% female Twice daily: 42% female • Average age Once daily: median 63 years (range 34 - 80) Twice daily: median 61 years (range 30 - 82) Interventions • Radiotherapy	allocation. Blinding of participants and personnel • High risk of bias Unlikely any blinding was done Blinding of outcome assessment • High risk of bias Unlikely any blinding was done Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Balanced groups Overall risk of bias • Moderate Likely to have been Non-blinded, allocation concealment procedures unclear. Directness • Partially directly applicable Study took place before 2000 with more recent studies of this nature using higher dose radiotherapy.

Study	Title	Study characteristics	Risk of bias
		Once daily: 45 Gy (25 x 1.8 Gy) over 5 weeks. Twice daily: 45 Gy (30 x 1.5 Gy) over 3 weeks. All patients received prophylactic cranial irradiation lasting 12 weeks • Chemotherapy "patients received four cycles of chemotherapy. Each three-week cycle consisted of 60 mg of cisplatin per square meter of body-surface area on day 1 and 120 mg of etoposide per square meter on days 1, 2, and 3." Outcome measures • Survival Overall, disease-progression free • Adverse events (grade 3 or above) Myelotoxicity (decrease in marrow-derived cells in peripheral blood counts), esophagitis, other, weight loss, fever, vomiting, pulmonary effects, infection, anaemia, thrombocytopenia, granulocytpoenia, leukopenia.	