Appendix E – Clinical evidence tables

Short Title	Title	Study Characteristics	Risk of Bias
Albain 2009	Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial	**Study type** • Randomised controlled trial **Study details** • Study location *USA and Canada* • Study setting *Hospitals* • Study dates *Recruitment was between 1994 to 2001* • Duration of follow-up *A minimum of 2.5 years. Participants were followed every 2 months for 1 year, every 3 months for 2 years, then every 6 months indefinitely. The median follow-up was 22.5 months.* • Sources of funding *National Cancer Institute and the Canadian Cancer Society.* **Inclusion criteria** • Pathologic proof of N2 involvement *All patients had stage IIIA (pN2) disease: T1, T2 or T3 primary NSCLC. If contralateral mediastinal nodes larger than 1 cm were visible on the CT scan, biopsy was required to exclude N3 (stage IIIB) disease.* • Staging CT of chest, abdomen, head *CT brain or MRI brain* • Potentially resectable **Exclusion criteria**	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias No blinding. However, this is probably not possible. Blinding of participants and personnel • Unclear risk of bias No blinding. However, this is probably not possible. Blinding of outcome assessment • Unclear risk of bias No blinding. However, this is probably not possible. 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

Short Title	Title	Study Characteristics	Risk of Bias
		• If overall FEV1 was less than 2000 cc, a predicted post-resection FEV1 of <800 cc • Karnofsky performance status <90 • If Karnofsky performance status 70 or 80, albumin <0.85 x normal or weight loss >10% within previous 3 months **Sample characteristics** • Sample size *396 people* • Split between study groups *Induction chemotherapy + radiotherapy, followed by surgery = 202; Induction chemotherapy + radiotherapy = 194* • Loss to follow-up *None were lost to follow-up. However, of the 202 people in the surgery arm, 9 did not have surgery. There was no explanation given.* • % female *Induction chemotherapy + radiotherapy, followed by surgery = 35.1%; Induction chemotherapy + radiotherapy = 37.6%* • Average age *Median (range): Induction chemotherapy + radiotherapy, followed by surgery = 59 (31-77); Induction chemotherapy + radiotherapy = 61 (32-78)* **Interventions** • Chemoradiotherapy, surgery *The induction chemoRT was cisplatin (50 mg/m2 days 1, 8, 29, 36), and etoposide (50 mg/m2 days 1-5 and 29-33), plus 45 Gy thoracic RT beginning day 1, in 1.8 Gy daily fractions. Disease re-evaluation by CT scan plus repeat pulmonary function tests was done 2-4 weeks after completion of RT. If there was no disease progression and the patient remained medically fit, a complete surgical resection (with protocol-specified mediastinal lymph node sampling/dissection) was performed*	Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		3-5 weeks after completion of RT. Patients received 2 cycles of consolidation chemotherapy (same doses and schedule as during induction). Dose reduction guidelines were specified for chemoRT, with central quality control. A chest CT scan was scheduled 4-6 weeks after completion of the last chemotherapy cycle. Patients were followed every 2 months for 1 year, every 3 months for 2 years, then every 6 months indefinitely. CT scans of the thorax and upper abdomen and MRI or CT of the brain were done at 12, 18, and 24 months and annually thereafter. • Chemoradiotherapy *The induction chemoRT was cisplatin (50 mg/m2 days 1, 8, 29, 36), and etoposide (50 mg/m2 days 1-5 and 29-33), plus 45 Gy thoracic RT beginning day 1, in 1.8 Gy daily fractions. Disease re-evaluation by CT scan plus repeat pulmonary function tests was done 7 days before completion of induction chemoRT. If there was no disease progression and the patient remained medically fit, the RT was continued to 61 Gy. Patients received 2 cycles of consolidation chemotherapy (same doses and schedule as during induction). Dose reduction guidelines were specified for chemoRT, with central quality control. A chest CT scan was scheduled 4-6 weeks after completion of the last chemotherapy cycle. Patients were followed every 2 months for 1 year, every 3 months for 2 years, then every 6 months indefinitely. CT scans of the thorax and upper abdomen and MRI or CT of the brain were done at 12, 18, and 24 months and annually thereafter.* **Outcome measures** • Mortality, all-cause • Adverse events grade 3 or above	
Eberhardt 2015	Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients	**Study type** • Randomised controlled trial **Study details** • Study location	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment

Short Title	Title	Study Characteristics	Risk of Bias
	With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE)	*Germany* • Study setting *Hospitals* • Study dates *Recruitment was from 2004 to 2013* • Duration of follow-up *Follow-up visits were scheduled every 3 months after random assignment. Follow-up was a minimum of 1 year.* • Sources of funding *German Cancer Aid* **Inclusion criteria** • Pathologically proven NSCLC • Potentially resectable stage IIIA(N2) or selected stage IIIB *N2 disease had to be pathologically proven during mediastinoscopy (recommended), endobronchial ultrasonography, or parasternal mediastinotomy. Selected resectable IIIB disease was defined as N3 disease with contralateral mediastinal nodes and proven T4 disease with involvement of the pulmonary artery, carina, left atrium, vena cava, or mediastinum. Positron emission tomographic (PET) or PET–computed tomographic staging, which was performed in 97%, and brain imaging investigations were routinely recommended.* **Exclusion criteria** • ECOG performance status 2 or above • >10% weight loss in the 6 months before diagnosis • Inadequate renal, hepatic or haematologic functions **Sample characteristics** • Sample size *161 people*	• Unclear risk of bias No blinding. However, this is probably not possible in this instance. Blinding of participants and personnel • Unclear risk of bias No blinding. However, this is probably not possible in this instance. Blinding of outcome assessment • Unclear risk of bias No blinding. However, this is probably not possible in this instance. 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 Directness • Partially directly applicable 30% in the surgery arm and 35% in the non-surgery arm were T4, N0 or N1. (They were not N2)

Short Title	Title	Study Characteristics	Risk of Bias
		• Split between study groups *Induction chemotherapy, chemoradiotherapy + surgery = 81; induction chemotherapy, chemoradiotherapy = 80* • Loss to follow-up *None* • %female *Induction chemotherapy, chemoradiotherapy + surgery = 31%; induction chemotherapy, chemoradiotherapy = 34%* • Average age *Median (range): Induction chemotherapy, chemoradiotherapy + surgery = 58 years (33-72); induction chemotherapy, chemoradiotherapy = 59 years (42-74)* **Interventions** • Chemotherapy, chemoradiotherapy + surgery *Induction chemotherapy consisted of three cycles of dose-dense cisplatin and paclitaxel in a 21-day cycle. Neoadjuvant radiotherapy was delivered to a total cumulative dose of 45 Gy, as two 1.5-Gy fractions per day, given 5 days a week. The minimum interval between daily fractions was 6 hours. Three dimensional treatment planning was mandatory. Intensity-modulated radiotherapy was not allowed. Concurrent chemotherapy consisted of one cycle of cisplatin and vinorelbine: cisplatin 50 mg/m2 on days 2 and 9 and vinorelbine 20 mg/m2 on days 2 and 9 of neoadjuvant radiotherapy.* • Chemotherapy, chemoradiotherapy boost *Induction chemotherapy consisted of three cycles of dose-dense cisplatin and paclitaxel in a 21-day cycle. Neoadjuvant radiotherapy was delivered to a total cumulative dose of 45 Gy, as two 1.5-Gy fractions per day, given 5 days a week. The minimum interval between daily fractions was 6 hours. Three dimensional treatment planning was mandatory. Intensity-modulated radiotherapy was not allowed. Concurrent chemotherapy consisted of one cycle of cisplatin and vinorelbine: cisplatin 50 mg/m2 on days 2 and 9 and vinorelbine 20*	

Short Title	Title	Study Characteristics	Risk of Bias
		mg/m2 on days 2 and 9 of neoadjuvant radiotherapy. The chemoradiotherapy boost was risk adapted to between 65 and 71 Gy. This was done in the following way: Definitive boost radiotherapy was given at 2 Gy per fraction, five fractions per week, to a cumulative dose of 20 to 26 Gy without a treatment break from neoadjuvant radiotherapy. A 26-Gy boost dose was recommended if deliverable within the normal tissue constraints. Specific radiation parameters, techniques, concurrent chemotherapy application given to the boost (cisplatin 40 mg/m2 on day 2 and vinorelbine 15mg/m2 on days 2 and 9 of the boost radiotherapy). The maximum allowed mean dose to the lung was 18 Gy, and the maximum dose at the spinal cord had to be less than 42 Gy. To avoid increased toxicities during the concurrent chemoradiotherapy boost, and given the previous experience in the pilot phase II study, concurrent chemotherapy to the boost was reduced in doses of cisplatin and vinorelbine. **Outcome measures** • Mortality, all-cause • Adverse events grade 3 or above • Dropout during treatment	
Girard 2010	Is neoadjuvant chemoradiotherapy a feasible strategy for stage IIIA-N2 non-small cell lung cancer? Mature results of the randomized IFCT-0101 phase II trial	**Study type** • Randomised controlled trial **Study details** • Study location *France* • Study setting *Hospitals* • Study dates *Recruitment was from 2003 to 2007* • Duration of follow-up *Median follow-up of 31.4 months.*	**Quality assessment (RCT)** Random sequence generation • High risk of bias Randomization was stratified by clinical centre and histological type (squamous cell carcinoma vs. others). However, the 3 groups were not balanced in terms of gender or pN2/cN2. This might be because of the relatively low numbers of participants. Nevertheless, they were not balanced. Allocation concealment • Unclear risk of bias Blinding is probably not possible in this sort of study.

Short Title	Title	Study Characteristics	Risk of Bias
		• Sources of funding *Programme Hospitalier de Recherche Clinique, Ligue National contre le Cancer and the Lilly Laboratories.* **Inclusion criteria** • Staging CT of chest, abdomen, head *CT brain or MRI brain. Fiberoptic bronchoscopy, mediastinoscopy.* • Pathologically proven NSCLC • Stage IIIA (T1-3)-N2 • Potentially resectable **Exclusion criteria** • ECOG performance status 2 or above • Inadequate renal, hepatic or haematologic functions • Age <18 years • Age >70 years • Unsatisfactory medical condition for chemotherapy, thoracic radiotherapy and surgery • Predicted post-operative FEV1 <35% of predicted value • High probability of stage IIIB NSCLC *In other words, if the tumour was suspected to invade the carina, the superior vena cava, the phrenic nerves, the aorta, the oesophagus, the vertebrae, the heart, the chest wall, or the contra-lateral mediastinal or supra-clavicular lymph nodes.* • Previous chemotherapy or thoracic radiotherapy • History of respiratory, cardiac failure, or invasive cancer **Sample characteristics** • Sample size *46 people* • Split between study groups	Blinding of participants and personnel • Unclear risk of bias Blinding is probably not possible in this sort of study. Blinding of outcome assessment • Unclear risk of bias Blinding is probably not possible in this sort of study. 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 Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Induction chemotherapy, surgery = 14; induction chemoradiotherapy (cisplatin + vinorelbine), surgery = 17; induction chemoradiotherapy (carboplatin + paclitaxel), surgery = 15 • Loss to follow-up *None* • %female *Induction chemotherapy, surgery = 35.7%; induction chemoradiotherapy (cisplatin + vinorelbine), surgery = 11.8%; induction chemoradiotherapy (carboplatin + paclitaxel), surgery = 13.3%* • Average age *Not provided* • Numbers of participants with pN2 and cN2 *Induction chemotherapy, surgery = 6 & 8; induction chemoradiotherapy (cisplatin and vinorelbine), surgery = 15 & 2; induction chemoradiotherapy (carboplatin and paclitaxel), surgery = 12 & 3* **Interventions** • Chemotherapy, surgery *This arm consisted of chemotherapy with cisplatin (80mg/m2 on days 1, 22, 43) and gemcitabine (1250mg/m2 on days 1, 8, 22, 29, 43, 50). Surgery was scheduled between week 11 and week 14 after randomisation. Lobectomy or pneumonectomy was performed. After surgery, post-operative treatment depended on the completion of the resection. In case of complete resection (R0), no adjuvant treatment was administered; in case of microscopically incomplete resection (R1), adjuvant radiotherapy was done to a total dose of 60 Gy for patients assigned this arm. After macroscopically incomplete resection (R2), radiotherapy was administered to a total dose of 60 Gy after a pneumonectomy, and of 66Gy after a lobectomy for patients in this arm.* • Chemoradiotherapy (cisplatin + vinorelbine), surgery *Participants received induction chemotherapy followed by chemoradiotherapy. This arm consisted of the combination of cisplatin*	

Short Title	Title	Study Characteristics	Risk of Bias
		(80mg/m2 on days 1, 22, 43) and vinorelbine (25mg/m2 on days 1, 8, 15, and 15mg/m2 on days 22, 29, 43, 50), with radiotherapy to a total dose of 46 grays delivered from week 4 to week 8. Conformal radiotherapy was delivered using a standard fractionation scheme (2 Gy/day, 5 days/week), after a three-dimensional treatment planning. Patients were immobilized using a cervico-thoracic immobilization device. The gross tumor volume (GTV) was defined as the primary tumor mass including any hilar or mediastinal lymph node ≥1 cmin short axis dimension. A 6–8mmmargin was added to the GTV to account for microscopic extension. Additional margins for tumor motion, ranging from 10 to 20mm were added based on radioscopy to define the Planned Tumor Volume (PTV). Dose–volume histograms for normal lung were calculated using total lung volume excluding the PTV. The lung V20 had to be lower than 30%. Total dose to the spinal cord was limited to 46 Gy. The maximal dose delivered to more than 15cm of the oesophagus was 40 Gy. Treatment plans included corrections for lung tissue inhomogeneity. The 100%-isodose line was defined at the isocenter of the treatment plan, and total dose was prescribed to this point. Beam-eye-view display was used to ensure optimal target volume coverage and normal tissue sparing. After surgery, post-operative treatment depended on the completion of the resection. In case of complete resection (R0), no adjuvant treatment was administered; in case of microscopically incomplete resection (R1), a dose of 14 Gy was delivered post-operatively. After macroscopically incomplete resection (R2), radiotherapy was administered to a total dose of 60 Gy after a pneumonectomy. For patients initially assigned to this arm, the decision about adjuvant treatment was left to the discretion of the local investigator. *• Chemoradiotherapy (carboplatin + paclitaxel), surgery* *Participants received induction chemotherapy followed by chemoradiotherapy. This arm consisted of the association of carboplatin (Calvert AUC 6 on day 1, and AUC 2 on days 22, 29, 36, 43, 50) and paclitaxel (200mg/m2 on day 1, and 40mg/m2 on days 22, 29, 36, 43, 50), with radiotherapy to a total dose of 46 grays delivered from week 4 to week 8. Conformal radiotherapy was delivered using a*	

Short Title	Title	Study Characteristics	Risk of Bias
		standard fractionation scheme (2 Gy/day, 5 days/week), after a three-dimensional treatment planning. Patients were immobilized using a cervico-thoracic immobilization device. The gross tumour volume (GTV) was defined as the primary tumour mass including any hilar or mediastinal lymph node ≥1 cmin short axis dimension. A 6–8mmmargin was added to the GTV to account for microscopic extension. Additional margins for tumour motion, ranging from 10 to 20mm, were added based on radioscopy to define the Planned Tumour Volume (PTV). Dose–volume histograms for normal lung were calculated using total lung volume excluding the PTV. The lung V20 had to be lower than 30%. Total dose to the spinal cord was limited to 46 Gy. The maximal dose delivered to more than 15cm of the oesophagus was 40 Gy. Treatment plans included corrections for lung tissue inhomogeneity. The 100%-isodose line was defined at the isocenter of the treatment plan, and total dose was prescribed to this point. Beam-eye-view display was used to ensure optimal target volume coverage and normal tissue sparing. After surgery, post-operative treatment depended on the completion of the resection. In case of complete resection (R0), no adjuvant treatment was administered; in case of microscopically incomplete resection (R1), a dose of 14 Gy was delivered post-operatively. After macroscopically incomplete resection (R2), radiotherapy was administered to a total dose of 60 Gy after a pneumonectomy. For patients initially assigned to this arm, the decision about adjuvant treatment was left to the discretion of the local investigator. **Outcome measures** • Mortality, all-cause • Adverse events grade 3 or above	
Johnstone 2002	Phase III study comparing chemotherapy and radiotherapy with preoperative	**Study type** • Randomised controlled trial **Study details**	**Quality assessment (RCT)** Random sequence generation • High risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
	chemotherapy and surgical resection in patients with non-small-cell lung cancer with spread to mediastinal lymph nodes (N2); final report of RTOG 89-01. Radiation Therapy Oncology Group	• Study location *USA* • Study setting *Hospitals* • Study dates *1990 to 1994* • Duration of follow-up *Follow-up was for at least 48 months.* • Sources of funding *Not stated* **Inclusion criteria** • Pathologic proof of N2 involvement • Stage IIIA (T1-3)-N2 *And M0* **Exclusion criteria** • None **Sample characteristics** • Sample size *61 people* • Split between study groups *Induction chemotherapy, surgery = 29; induction chemotherapy, radiotherapy = 32* • Loss to follow-up *2 people. It is not specified which arms they were in.* • %female *Induction chemotherapy, surgery = 38%; induction chemotherapy, radiotherapy = 22%*	Some participants were not randomised but were included in the mortality results: 7/29 in the surgery arm and 9/32 in the radiotherapy arm. Allocation concealment • Unclear risk of bias No blinding. However, this may not be possible for these participants. Blinding of participants and personnel • Unclear risk of bias No blinding. However, this may not be possible for these participants. Blinding of outcome assessment • Unclear risk of bias No blinding. However, this may not be possible for these participants. Incomplete outcome data • High risk of bias There was a narrative description of the adverse events. However, there should have been a table because the investigators' definition of what is "equivalent" might not be the same as other people's definition of equivalence. Selective reporting • High risk of bias The mortality data included non-randomised participants. The mortality data might have been

Short Title	Title	Study Characteristics	Risk of Bias
		• Average age *Percentage <60 years, percentage 60+ years: Induction chemotherapy, surgery = 59%, 41%; induction chemotherapy, radiotherapy = 50%, 50%* **Interventions** • Chemotherapy, surgery *Induction chemotherapy consisted of cisplatin 120 mg/m2 on Days 1 and 29, vinblastine 4.5 mg/m2 on Days 1, 15, 29, and 43, and mitomycin-C 8 mg/m2 on Days 1 and 29. Patients were randomised to surgery on Day 71 followed by cisplatin on Days 99 and 127, vinblastine on Days 99, 113, 127, and 141. 7/29 participants were not randomised and had mitomycin-C in addition to the induction chemotherapy described above.* • Chemotherapy, radiotherapy *Induction chemotherapy consisted of cisplatin 120 mg/m2 on Days 1 and 29, vinblastine 4.5 mg/m2 on Days 1, 15, 29, and 43, and mitomycin-C 8 mg/m2 on Days 1 and 29. Participants were randomised to radiotherapy starting on Day 71, given to 64 Gy in 2.0 Gy fractions, followed by cisplatin on Days 141 and 169 and vinblastine on Days 141, 155, 169, and 183. 9/32 participants were not randomised and had mitomycin-C in addition to the induction chemotherapy described above. Radiotherapy (50 Gy at 2.0-Gy fractions/d, 5 fractions/wk) to the primary and regional nodes began 2–4 weeks after the completion of induction chemotherapy. A boost dose of 14 Gy was delivered at 2.0-Gy fractions/d, 5 fractions/wk, to gross disease as seen on the original CT scan, for a total dose of 64 Gy to all involved sites. All doses were calculated at the center of the target volume; the maximal dose could not exceed the target dose by >15%. The primary site and hilar/mediastinal nodes were treated with a 2-cm margin to a minimal dose of 50 Gy; the boost volume included only gross disease in these sites, with the fields defined by custom lead blocking. Beam energies >1 MeV were required, and posterior spinal*	different if only randomised participants had been included. Other sources of bias • High risk of bias The non-randomised participants that were included in the mortality data had different chemotherapy regimens compared to the randomised participants. Overall risk of bias • High Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		cord blocks were not allowed. All simulation and portal films were centrally reviewed for protocol compliance. **Outcome measures** • Mortality, all-cause	
Katakami 2012	A phase 3 study of induction treatment with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA nonsmall cell lung cancer (WJTOG9903)	**Study type** • Randomised controlled trial **Study details** • Study location *Japan* • Study setting *Multiple academic and community hospitals.* • Study dates *2000 to 2005* • Duration of follow-up *Patients were scheduled for a chest CT scan 4 to 6 weeks after completion of the last chemotherapy cycle and were followed up every 2 months for at least 5 years. During this time, the patients received CT scans of the chest and upper abdomen, CT or MRI scans of the brain, and bone scans every 6 months.* • Sources of funding *No specific funding was disclosed.* **Inclusion criteria** • Pathologic proof of N2 involvement *From biopsy samples of the ipsilateral mediastinal nodes that were visible on a CT scan.* • Staging CT of chest, abdomen, head *Also included a bone scan. CT brain or MRI brain.* • Pathologically proven NSCLC	**Quality assessment (RCT)** Random sequence generation • Unclear risk of bias The randomisation method was not provided. However, the baseline characteristics of both arms were roughly equal. Allocation concealment • Unclear risk of bias There was no blinding in this study. However, blinding might not be realistically possible for these participants. Blinding of participants and personnel • Unclear risk of bias There was no blinding in this study. However, blinding might not be realistically possible for these participants. Blinding of outcome assessment • Unclear risk of bias There was no blinding in this study. However, blinding might not be realistically possible for these participants. Incomplete outcome data

Short Title	Title	Study Characteristics	Risk of Bias
		• Stage IIIA (T1-3)-N2 • Potentially resectable **Exclusion criteria** • ECOG performance status 2 or above • Inadequate renal, hepatic or haematologic functions *And unsatisfactory cardiac function.* • Age >70 years • Partial pressure of arterial oxygen <70 Torr • FEV1 <1.5 L • Prior malignancy other than non-melanoma skin cancer or adequately treated stage I in situ cervical cancer • Uncontrolled angina pectoris or a history of congestive heart failure or myocardial infarction within 3 months • Pulmonary fibrosis detectable by CT scan • COPD (FEV1 <65%) • >10% weight loss within the previous 6 months • Age <20 years **Sample characteristics** • Sample size *56 people* • Split between study groups *Induction chemotherapy, surgery = 29; induction chemoradiotherapy, surgery = 31* • Loss to follow-up *None* • %female *Induction chemotherapy, surgery = 32%; induction chemoradiotherapy, surgery = 34%* • Average age	• Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Median age (range): Induction chemotherapy, surgery = 58.0 years (34-69); induction chemoradiotherapy, surgery = 57.0 years (36-70) **Interventions** • Chemotherapy, surgery *Induction chemotherapy involved 2 cycles of carboplatin (area under the receiver operating curve [AUC] = 5 on days 1, 22, intravenous infusions) and docetaxel (60 mg/m2 on days 1, 22, intravenous infusions). The patients were reassessed using CT scan plus repeat pulmonary function tests 2 to 4 weeks after completion of the induction therapy. The response to induction was assessed by WHO criteria without the need for a second confirmation of response. If the disease had not progressed and the patient remained medically healthy, a complete surgical resection with a mediastinal lymph node dissection was performed 3 or 4 weeks after the induction therapy was completed. No consolidation chemotherapy was administered after surgery. Dose reduction guidelines were specified in the protocol.* • *Chemoradiotherapy (carboplatin + docetaxel), surgery* *Induction chemotherapy involved 2 cycles of carboplatin (area under the receiver operating curve [AUC] = 5 on days 1, 22, intravenous infusions) and docetaxel (60 mg/m2 on days 1, 22, intravenous infusions). Thoracic radiotherapy (40 Gy in 20 fractions of 2 Gy over 4 weeks) was also administered from day 1. All patients were treated with a linear accelerator photon beam of 6MV or more. At the commencement of this multi-institutional study, a 3-dimensional (3D) treatment planning system using CT was not available at some of the participating institutions. Hence, 2-dimensional (2D) treatment planning techniques were allowed. Radiation doses were specified at the centre of the target volume, and doses were calculated assuming tissue homogeneity without correction for lung tissues. The primary tumour and involved nodal disease received 40 Gy in 2 Gy fractions over 4 weeks via the anterior and posterior opposing portals. Radiation fields included the primary tumour with a margin of at least 1.0 cm, and the ipsilateral hilum and mediastinal nodal areas with a margin of 0.5 to 1.0*	

Short Title	Title	Study Characteristics	Risk of Bias
		cm from the paratracheal lymph nodes (#2) to 4.5 cm below the tracheal bifurcation including subcarinal lymph nodes (#7). The contralateral hilum was not included. The supraclavicular areas were not treated routinely, but the ipsilateral supraclavicular area was treated when the primary tumour was located in the upper lobe. The patients were reassessed using CT scan plus repeat pulmonary function tests 2 to 4 weeks after completion of the induction therapy. The response to induction was assessed by WHO criteria without the need for a second confirmation of response. If the disease had not progressed and the patient remained medically healthy, a complete surgical resection with a mediastinal lymph node dissection was performed 3 or 4 weeks after the induction therapy was completed. No consolidation chemotherapy was administered after surgery. Dose reduction guidelines were specified in the protocol. Patients in the CRS arm who could not be treated surgically within 6 weeks after induction therapy received further radiotherapy of up to 66 Gy in 33 fractions in total. In this boost radiotherapy procedure, the spinal cord was excluded from the radiation fields. **Outcome measures** • Mortality, all-cause • Adverse events grade 3 or above	
Pless 2015	Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial	**Study type** • Randomised controlled trial **Study details** • Study location *Switzerland, Germany and Serbia* • Study setting *Cancer centres* • Study dates *Enrolment was from 2001 to 2012*	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias There was no blinding. However, blinding may not be realistically possible with these participants. Blinding of participants and personnel • Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		• Duration of follow-up *Patients attended follow-up visits 1 month after surgery, then every 3 months for 2 years, every 6 months for 2 years, and then every 12 months. During visits patients were assessed for toxic effects. They also underwent chest radiography or chest CT at alternate visits for 5 years. The trial was stopped after the third interim analysis and 134 events, on the advice of the independent data monitoring board, because the futility boundary had been crossed. At the time of data cut-off, the median follow-up time was 52·4 months (IQR 32·0–85·2).* • Sources of funding *This study was funded by the Swiss State Secretariat for Education, Research and Innovation, the Swiss Cancer League and Sanofi.* **Inclusion criteria** • Pathologic proof of N2 involvement *Participants with histological or cytological proof of non-small-cell lung cancer but N2 lymph nodes not accessible to biopsy (eg, aortic node regions 5 and 6) were eligible, provided that the N2 node had a diameter greater than 1 cm and was PET positive, and the N3 nodes had diameters less than 1 cm and were PET negative.* • Pathologically proven NSCLC • Stage IIIA (T1-3)-N2 *And M0* • Staging PET-CT and brain MRI **Exclusion criteria** • ECOG performance status 2 or above • Age <18 years • Age >75 years • Unacceptable lung and cardiac function according to local standards • Inadequate liver, bone marrow and kidney functions *Creatinine clearance less than 1·00 mL/s [60 mL/min]*	There was no blinding. However, blinding may not be realistically possible with these participants. Blinding of outcome assessment • Unclear risk of bias There was no blinding. However, blinding may not be realistically possible with these participants. 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 Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Sample characteristics • Sample size *231 people* • Split between study groups *Induction chemotherapy, surgery = 115; induction chemoradiotherapy, surgery = 117* • Loss to follow-up *Induction chemotherapy, surgery = 8; induction chemoradiotherapy, surgery = 2* • %female *Induction chemotherapy, surgery = 33%; induction chemoradiotherapy, surgery = 33%* • Average age *Median age (range): Induction chemotherapy, surgery = 59.0 years (30.0-74.0); induction chemoradiotherapy, surgery = 60.0 years (37.0-76.0)* **Interventions** • Chemotherapy, surgery *Chemotherapy consisted of three cycles of 100 mg/m² intravenous cisplatin and 85 mg/m² docetaxel given every 3 weeks. The administration of prophylactic granulocyte-colony stimulating factor was compulsory. Dose reductions were not allowed for cisplatin. Switch to carboplatin (target area under the curve 6) was possible if patients developed renal insufficiency (creatinine clearance lower than 0·83 mL/s [50 mL/ min]), hearing loss worse than grade 1, or peripheral neuropathy worse than grade 2. Dose reductions for docetaxel to 55 mg/m² were possible if patients developed impaired liver function (worse than grade 1), grade 3 diarrhoea, or peripheral neuropathy (worse than grade 1). If toxic effects did not recover to grade 1 severity or resolve within 2 weeks, chemotherapy was stopped. Surgery was scheduled 21 days after the last chemotherapy cycle for patients in the*	

Short Title	Title	Study Characteristics	Risk of Bias
		chemotherapy group. Surgery included tumour resection and systematic lymph node dissection. Patients in the chemotherapy group in whom resection was incomplete (R1 or R2) were allowed to receive postoperative radiotherapy. • Chemoradiotherapy (cisplatin + docetaxel), surgery *Chemotherapy consisted of three cycles of 100 mg/m² intravenous cisplatin and 85 mg/m² docetaxel given every 3 weeks. The administration of prophylactic granulocyte-colony stimulating factor was compulsory. Dose reductions were not allowed for cisplatin. Switch to carboplatin (target area under the curve 6) was possible if patients developed renal insufficiency (creatinine clearance lower than 0·83 mL/s [50 mL/ min]), hearing loss worse than grade 1, or peripheral neuropathy worse than grade 2. Dose reductions for docetaxel to 55 mg/m² were possible if patients developed impaired liver function (worse than grade 1), grade 3 diarrhoea, or peripheral neuropathy (worse than grade 1). If toxic effects did not recover to grade 1 severity or resolve within 2 weeks, chemotherapy was stopped. Three weeks after day 1 of the last planned date of chemotherapy, radiotherapy was started in patients in the chemoradiotherapy group. Patients received 44 Gy in 22 fractions over a 3 week period, delivered with a concomitant boost technique. Planning target volumes were defined according to the results of CT scans done after induction chemotherapy. Planning target volume 1, representing the original volume, included the primary tumour, lymph nodes, ipsilateral hilus, and ipsilateral and contralateral mediastinum at risk of subclinical disease, with a 1·5–2·0 cm margin. Planning target volume 2 included the primary tumour (gross disease) with a 1·5–2·0 cm margin and lymph node metastases in the mediastinum and represented the boost volume. Arrangement of fields was at the discretion of the investigators as long as the target volumes were clearly outlined. The dose to the spinal cord had to remain lower than 36 Gy. The prescribed dose was specified at the International Commission on Radiation Units and Measurements reference point. Computer assisted three-dimensional treatment planning was used in all cases, and the selection of a collapsed cone or Monte Carlo algorithm was recommended for photon*	

Short Title	Title	Study Characteristics	Risk of Bias
		energies greater than 6 MV. The reference isodose had to be within 10% of that prescribed, and hot spots were delineated and recorded. Central review of three random patients from each centre was done to ensure radiotherapy quality control. Surgery was scheduled 21–28 days after completion of radiotherapy for patients in the chemoradiotherapy group. Surgery included tumour resection and systematic lymph node dissection. **Outcome measures** • Mortality, all-cause • Adverse events grade 3 or above	
Shepherd 1998	Randomized study of chemotherapy and surgery versus radiotherapy for stage IIIA non-small-cell lung cancer: a National Cancer Institute of Canada Clinical Trials Group Study	**Study type** • Randomised controlled trial **Study details** • Study location *Canada* • Study setting *Hospital* • Study dates *Not provided. This study was received by the publishers in 1997.* • Duration of follow-up *Looking at the survival chart, participants were followed up for 24 months in the radiotherapy arm and 31 months in the surgery arm.* • Sources of funding *Not stated* **Inclusion criteria** • Stage IIIA N2 NSCLC with biopsy-proven mediastinal node involvement	**Quality assessment (RCT)** Random sequence generation • High risk of bias Method of randomisation was not given. In addition, the median age of participants was 9 years older in the chemotherapy, surgery group compared to the radiotherapy group. Allocation concealment • Unclear risk of bias There was no blinding in this study. However, blinding may not have been realistically possible due to the nature of the condition. Blinding of participants and personnel • Unclear risk of bias There was no blinding in this study. However, blinding may not have been realistically possible due to the nature of the condition. Blinding of outcome assessment

Short Title	Title	Study Characteristics	Risk of Bias
		Exclusion criteria • Stage IIIB • Not able to tolerate planned surgery • Post-operative predicted FEV1 <0.8 L • ECOG performance status >2 • Haemoglobin <100 g/L • Granulocytes <2.0 x 109 /L • Platelets <100 x 109 /L • Serum creatinine >150 micro mol / L • Liver enzymes >1.25 x upper limit of normal **Sample characteristics** • Sample size *31 people* • Split between study groups *Chemotherapy, surgery = 16; radiotherapy = 15* • Loss to follow-up *None* • %female *Chemotherapy, surgery = 25%; radiotherapy = 33%* • Average age *Median (range): chemotherapy, surgery = 61 years (49-70); radiotherapy = 52 years (44-72)* **Interventions** • Chemotherapy, surgery *Patients received cisplatin 120 mg m2 on days 1 and 29 and vinblastine 6 mg m2 on days 1. 15. 22. 29 and 43. Cisplatin was administered in hospital with vigorous hydration and mannitol diuresis and dexamethasone. Ondansetron and lorazepam were given to prevent vomiting. Patients proceeded to surgery between days 51 and*	• Unclear risk of bias There was no blinding in this study. However, blinding may not have been realistically possible due to the nature of the condition. Incomplete outcome data • High risk of bias A narrative description of adverse events was given in such a way that it is not possible to compare groups. For example, there was either no grading or no participant numbers provided and it is not clear which adverse events occurred in which arm. A table of adverse events was not provided. Median survival in both arms was provided. However, follow-up lasted for 32 months and about 1/3 of participants were still alive at this time. Selective reporting • High risk of bias A narrative description of adverse events was given in such a way that it is not possible to compare groups. For example, there was either no grading or no participant numbers provided and it is not clear which adverse events occurred in which arm. A table of adverse events was not provided. Median survival in both arms was provided. However, follow-up lasted for 32 months and about 1/3 of participants were still alive at this time. Other sources of bias • Low risk of bias Overall risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		64 if they achieved partial or complete response or stable disease after chemotherapy. An attempt was made to excise all tissue felt to have been involved before chemotherapy and radical lymph node dissection was required. Patients who had complete resection received the same chemotherapy starting 6 weeks post-operatively. • Radiotherapy *A total dose of 60 Gy was planned to be riven as 2 Gy daily 5 days a week with the dose prescribed to the centre of the target volume (ICRU 29). The initial target volume (50 Gy) included the primary tumour and ipsilateral hilar, subcarinal, tracheobronchial and paratracheal nodes. The reduced target volume (10 Gy) included the tumour and involved nodes as determined by computerized tomography or mediastinoscopy. The spinal cord dose was limited to 48 Gy and real time review was performed.* **Outcome measures** • Mortality, all-cause • Dropout during treatment	• High Directness • Directly applicable
Stephens 2005	A randomised controlled trial of pre-operative chemotherapy followed, if feasible, by resection versus radiotherapy in patients with inoperable stage T3, N1, M0 or T1-3, N2, M0 non-small cell lung cancer	**Study type** • Randomised controlled trial **Study details** • Study location *UK* • Study setting *Christie Hospital NHS Trust, Manchester* • Study dates *Randomisation occurred between 1995 to 1999* • Duration of follow-up *The SF-36 quality of life questionnaire was used at baseline, 12 weeks and at 6 months. Adverse events were measured for the first 6 months.*	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias No blinding. However, blinding these participants and the staff involved with them may not be realistically possible. Blinding of participants and personnel • Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		Of the 48 patients, 39 died. The median follow-up for the 9 survivors was 14 months (range 5—68 months). • Sources of funding *Not provided. However, the MRC Clinical Trials Unit co-ordinated and analysed the results of the trial.* **Inclusion criteria** • NSCLC (T3, N1, M0 or T1-3, N2, M0) • Currently unresectable but have the potential to become resectable following chemotherapy • Thoracotomy or CT thorax & abdomen + mediastinoscopy or mediastinotomy **Exclusion criteria** • Not able to tolerate planned surgery • WHO performance status >2 • Creatinine clearance <50 ml/min • Full blood count outside the normal range • Previous or current other malignancy • Other disease or condition likely to interfere with the protocol treatments or comparisons • Contraindications to either of the treatment regimens **Sample characteristics** • Sample size *48 people* • Split between study groups *Chemotherapy, surgery = 24; radiotherapy = 24* • Loss to follow-up *None* • %female	No blinding. However, blinding these participants and the staff involved with them may not be realistically possible. Blinding of outcome assessment • Unclear risk of bias No blinding. However, blinding these participants and the staff involved with them may not be realistically possible. Incomplete outcome data • High risk of bias With the exception of lethargy, it was not possible to compare the other adverse events. This is because numbers and grades were not provided for each arm. In addition, quality of life data for each arm was not provided (it was only narratively described in the vaguest terms, e.g. – no statistically significant differences). Selective reporting • High risk of bias With the exception of lethargy, it was not possible to compare the other adverse events. This is because numbers and grades were not provided for each arm. In addition, quality of life data for each arm was not provided (it was only narratively described in the vaguest terms, e.g. – no statistically significant differences). Other sources of bias • Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		Chemotherapy, surgery = 29%; radiotherapy = 38% • Average age *Median (range): chemotherapy, surgery = 58 years (44-76); radiotherapy = 61 years (42-71)* **Interventions** • Chemotherapy, surgery *Chemotherapy, surgery patients received 4 cycles of chemotherapy at 3-week intervals with either MVP (mitomycin 6mg/m2 by IV injection, vinblastine 6mg/m2 by IV injection (maximum dose 10 mg), and cisplatin 50mg/m2 by IV infusion over 4 hours) or MIC (mitomycin 6mg/m2 by IV injection, ifosfamide 3 g/m2 by IV injection, with mesna, and cisplatin 50mg/m2 by IV infusion over 1 hour), with standard hydration and anti-emetics. Surgical resection, if considered feasible, was carried out between 4 and 6 weeks after the final cycle of chemotherapy. The surgical technique was decided by the local surgeon according to the site and extent of the tumour and local practice. Patients considered to have unresectable disease following chemotherapy received thoracic radiotherapy, the details of which were decided by the local radiation oncologist. One patient was withdrawn from the trial, and so the data below relate to 23 patients. Twenty-one patients were treated with MIC and two with MVP; 21 received all four cycles and two three cycles. Only four patients were treated surgically (two pneumonectomies), one lobectomy, one sleeve resection), although three further patients had a thoracotomy but did not proceed to resection. The 16 remaining patients were all reported to have progressive disease post-chemotherapy, although it may be that most of these patients simply did not respond sufficiently to be considered for resection. Of the 19 patients whose tumour was not resected, 13 received radiotherapy.* • Radiotherapy *Radiotherapy participants received thoracic radiotherapy, the details of which were to be decided by the local radiation oncologist according to the site and extent of the tumour and local practice, starting as soon as*	Overall risk of bias • High Directness • Partially directly applicable In the chemotherapy, surgery group, 4/24 were T3, N1, M0. In the radiotherapy group, 3/24 were T3, N1, M0 (not N2).

Short Title	Title	Study Characteristics	Risk of Bias
		possible after randomisation. It was recommended that the radiotherapy regimen be chosen in accordance with the recommendations of the 1994 Department of Health Standing Medical Advisory Committee, which stated that patients should receive 50—60 Gy to their tumour over a period of 3—6 weeks. Twenty of the 24 patients received radiotherapy, the commonest schedules used being 50 Gy/20f, 50 Gy/15f, 40 Gy/20f, 37 Gy/26f and 28 Gy/8f. The reasons for not receiving radiotherapy were: one patient refused treatment, one was considered unsuitable for radiotherapy, the diagnosis for one patient was changed to SCLC, and for the remaining patient the reason is not known. **Outcome measures** • Mortality, all-cause • Adverse events grade 2 or above *However, only enough data for a direct comparison was provided for lethargy.* • Dropout during treatment	
Thomas 2008	Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer	**Study type** • Randomised controlled trial **Study details** • Study location *Germany* • Study setting *Hospitals* • Study dates *Randomisation occurred between 1995 to 2003* • Duration of follow-up *After the end of treatment, follow-up assessments (physical assessment, chest radiography, abdominal ultrasonography, and blood chemistry) were done every 3 months for the first 2 years, then every 6*	**Quality assessment (RCT)** Random sequence generation • Unclear risk of bias Randomisation was done by a coordinating member in the Department of Medical Informatics. However, the method used was not described. Nevertheless, the baseline characteristics of both arms appear balanced. Allocation concealment • Unclear risk of bias There was no blinding. However, given the nature of the participants, blinding them and/or the staff may not be realistically possible.

Short Title	Title	Study Characteristics	Risk of Bias
		months. Additionally, for 5 years at every 6-month follow-up visit, a CT scan of the thorax was done. The median follow-up was 70 months. • Sources of funding *German Cancer Aid* **Inclusion criteria** • Pathologically proven NSCLC *Assessment of mediastinal lymph nodes by mediastinoscopy (occasionally by thoracoscopy, thoracotomy, or needle biopsy) was mandatory.* • Stage IIIA (T1-3, N2, M0) NSCLC • Stage IIIA (central T3, N0-1, M0) NSCLC • Stage IIIB (T4, N1-3, M0) NSCLC *T4 tumours were deemed potentially resectable if they involved the superior vena cava, left atrium, carina, distant trachea, or the great vessels.* • Stage IIIB (T1-4, N3, M0) NSCLC **Exclusion criteria** • ECOG performance status 2 or above • Age >70 years • Participants with T4 tumours with a malignant effusion, supraclavicular lymph node involvement, or invasion of the heart, oesophagus or vertebra. **Sample characteristics** • Sample size *524 people* • Split between study groups *Chemotherapy, chemoradiotherapy, surgery, radiotherapy = 264; chemotherapy, surgery, radiotherapy = 260*	Blinding of participants and personnel • Unclear risk of bias There was no blinding. However, given the nature of the participants, blinding them and/or the staff may not be realistically possible. Blinding of outcome assessment • Unclear risk of bias There was no blinding. However, given the nature of the participants, blinding them and/or the staff may not be realistically possible. Incomplete outcome data • High risk of bias The adverse events of leukocytopenia, thrombocytopenia and anaemia are not reported separately for each arm. In addition, many participants were missing adverse events data: chemotherapy, chemoradiotherapy, surgery, radiotherapy = 58/264; chemotherapy, surgery, radiotherapy = 73/260. Some adverse events may not have been reported altogether. For example, it's hard to believe that no participants experienced nausea or vomiting. Selective reporting • High risk of bias The adverse events of leukocytopenia, thrombocytopenia and anaemia are not reported separately for each arm. Some adverse events may not have been reported altogether. For example, it's

Short Title	Title	Study Characteristics	Risk of Bias
		• Loss to follow-up *Many participants were missing adverse events data: chemotherapy, chemoradiotherapy, surgery, radiotherapy = 58/264; chemotherapy, surgery, radiotherapy = 73/260.* • %female *Chemotherapy, chemoradiotherapy, surgery, radiotherapy = 18%; chemotherapy, surgery, radiotherapy = 17%* • Average age *Median (range): chemotherapy, chemoradiotherapy, surgery, radiotherapy = 59 years (33-69); chemotherapy, surgery, radiotherapy = 59 years (35-69)* **Interventions** • Chemotherapy, chemoradiotherapy, surgery, radiotherapy *In this arm, after three cycles of chemotherapy with cisplatin (55 mg/m²) and etoposide (100 mg/m²), patients without progressive disease (assessed with the same imaging techniques as used at baseline) were scheduled to continue with twice-daily radiotherapy and concurrent chemotherapy 3–5 weeks after the start of the third cycle of chemotherapy. All patients received CT-based three-dimensional planning. Two 1.5 Gy fractions per day, with an inter-treatment interval of at least 6 hours, were administered 5 days per week to a total dose of 45 Gy. The target volume included the primary lesion with margins of 1.5 cm, and the ipsilateral hilum and ipsilateral mediastinum extending inferiorly 5 cm below the tracheal bifurcation with a margin of 0.5–1 cm. For patients with N3 disease, the contralateral mediastinal lymph nodes, but not the contralateral hilum, were included with margins of 0.5 cm. Carboplatin (100 mg/m²) and vindesine (3 mg absolute) were administered once-weekly during treatment with twice-daily radiotherapy on days 1, 8, and 15 from the start of this phase. Surgery was scheduled 4–6 weeks after the completion of radiotherapy and concurrent chemotherapy in this arm. Extensive removal of the mediastinal lymph nodes was done, preferably by mediastinal lymph-node dissection (en-block removal of the mediastinal fatty tissue*	hard to believe that no participants experienced nausea or vomiting. Other sources of bias • High risk of bias Over 20% of participants were ‘lost to follow-up’ with regards to adverse events data: chemotherapy, chemoradiotherapy, surgery, radiotherapy = 58/264 (22%); chemotherapy, surgery, radiotherapy = 73/260 (28%). Overall risk of bias • High Directness • Indirectly applicable Participants who were N2 were in the minority: chemo, chemoradiotherapy, surgery = 17%; chemo, surgery = 12%.

Short Title	Title	Study Characteristics	Risk of Bias
		containing the lymphatics). Lymph-node levels to be removed were decided in accordance with the guidelines of the American Thoracic Society. If mediastinal lymph-node dissection was not done, at least mediastinal lymph-node sampling (removal or sampling of at least one lymph node) of the respective levels would have been done. Complete resection was defined as resection with negative margins and no metastatic involvement of the removed uppermost mediastinal lymph node. Histological diagnosis of the biopsies of the primary lesion and further histopathological assessment was done by the local pathologist and reviewed centrally by an experienced pneumopathologist. Also, mediastinal down-staging (initially documented N2 or N3 disease changing to N0 or N1 disease assessed by surgery) and tumour regression of more 90% was assessed centrally. Histopathological response was defined as fewer than 10% residual tumour cells in the sections of the primary lesion and no or only focal involvement with microscopic disease in the sections of mediastinal lymph nodes (tumour regression >90%). Patients deemed to have unresectable tumours or who were receiving an exploratory thoracotomy were scheduled to start twice-daily radiotherapy (total dose 24 Gy) as soon as possible after surgery. The target volume included the primary tumour with margins of 1.5 cm, the ipsilateral hilum, and ipsilateral mediastinum extending inferiorly 5 cm below the tracheal bifurcation with a margin of 0.5 to 1 cm. For patients with N3 disease, the contralateral mediastinal lymph nodes, but not the contralateral hilum, were included with margins of 0.5 cm. Additionally, patients with positive resection margins were given further radiotherapy (total dose 24 Gy). The target volume included the bronchial stump and the ipsilateral hilum. • Chemotherapy, surgery, radiotherapy *Participants had 3 cycles of chemotherapy with cisplatin (55 mg/m²) and etoposide (100 mg/m²). Surgery was scheduled after the third cycle of chemotherapy in this arm of the trial. Extensive removal of the mediastinal lymph nodes was done, preferably by mediastinal lymph-node dissection (en-block removal of the mediastinal fatty tissue containing the lymphatics). Lymph-node levels to be removed were*	

Short Title	Title	Study Characteristics	Risk of Bias
		decided in accordance with the guidelines of the American Thoracic Society. If mediastinal lymph-node dissection was not done, at least mediastinal lymph-node sampling (removal or sampling of at least one lymph node) of the respective levels would have been done. Complete resection was defined as resection with negative margins and no metastatic involvement of the removed uppermost mediastinal lymph node. Histological diagnosis of the biopsies of the primary lesion and further histopathological assessment was done by the local pathologist and reviewed centrally by an experienced pneumopathologist. Also, mediastinal down-staging (initially documented N2 or N3 disease changing to N0 or N1 disease assessed by surgery) and tumour regression of more 90% was assessed centrally. Histopathological response was defined as fewer than 10% residual tumour cells in the sections of the primary lesion and no or only focal involvement with microscopic disease in the sections of mediastinal lymph nodes (tumour regression >90%). Patients who were resected received conventionally fractionated radiotherapy (1.8 Gy per day) 4–6 weeks after surgery. All patients received CT-based three-dimensional planning. The target volume included the bronchial stump, the ipsilateral hilum, and ipsilateral mediastinum extending inferiorly 5 cm below the tracheal bifurcation with a margin of 0.5–1 cm. For patients with N3 disease, the contralateral mediastinal lymph nodes, but not the contralateral hilum, were included with margins of 0.5 cm. Patients with negative resection margins received a target volume dose of 54 Gy; those with positive margins received 68.4 Gy. Patients deemed unresectable or those with an exploratory thoracotomy were scheduled to start radiotherapy as soon as possible up to a total dose of 68.4 Gy. The target volume included the primary tumour with margins of 1.5 cm, the ipsilateral hilum, and ipsilateral mediastinum extending inferiorly 5 cm below the tracheal bifurcation with a margin of 0.5–1 cm. For patients with N3 disease, the contralateral mediastinal lymph nodes, but not the contralateral hilum, were included with margins of 0.5 cm. **Outcome measures** • Mortality, all-cause	

Short Title	Title	Study Characteristics	Risk of Bias
		• Adverse events grade 3 or above	
Van Meerbeeck 2007	Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer	**Study type** • Randomised controlled trial **Study details** • Study location *The Netherlands* • Study setting *Hospitals* • Study dates *Recruitment was from 1994 to 2002* • Duration of follow-up *Patients underwent follow-up visits every 3 months for 2 years and every 6 months thereafter, which included clinical evaluation, a chest-x-ray, and additional investigations when clinically indicated. The median follow-up was approximately 6 years.* • Sources of funding *National Cancer Institute. The study was supported by unrestricted educational grants of Eli Lilly, Bristol-Myers Squibb and Aventis.* **Inclusion criteria** • Pathologic proof of N2 involvement *Eligible patients had to have cytologic or histologic proof of unresectable stage IIIA-N2 NSCLC.* • Staging CT of chest, abdomen, head *Guidelines for unresectability were as follows: 1) any N2 involvement by a non-squamous carcinoma; 2) in case of squamous cell carcinoma, any N2 nodal involvement exceeding level 4R for a right-sided tumour and level 5 and 6 for a left-sided tumour. N2 found only at thoracotomy after a negative staging mediastinoscopy was not necessarily considered to be unresectable. Tumors and/or any involved	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias No blinding. However, it may not be realistically possible to blind participants and staff given the nature of the disease. Blinding of participants and personnel • Unclear risk of bias No blinding. However, it may not be realistically possible to blind participants and staff given the nature of the disease. Blinding of outcome assessment • Unclear risk of bias No blinding. However, it may not be realistically possible to blind participants and staff given the nature of the disease. Incomplete outcome data • High risk of bias The adverse events are reported narratively in such a way that it is not possible to compare the arms of the trial. It is hard to believe that no participant experienced nausea or vomiting. Selective reporting

Short Title	Title	Study Characteristics	Risk of Bias
		mediastinal lymph node(s) had to be unidimensionally measurable on CT scan. • Pathologically proven NSCLC **Exclusion criteria** • Age <18 years • Unsatisfactory medical condition for chemotherapy, thoracic radiotherapy and surgery • WHO performance status >2 • Previous or current other malignancy • Evidence of pulmonary fibrosis • Pre-existing neurotoxicity • Pre-existing infection • Previous therapy for NSCLC **Sample characteristics** • Sample size *308 people* • Split between study groups *Chemotherapy, surgery = 154; chemotherapy, radiotherapy = 154* • Loss to follow-up *None* • %female *Chemotherapy, surgery = 29%; chemotherapy, radiotherapy = 23%* • Average age *Median (range): chemotherapy, surgery = 61 years (29-78); chemotherapy, radiotherapy = 62 years (33-76)* **Interventions** • Chemotherapy, surgery	• High risk of bias The adverse events are reported narratively in such a way that it is not possible to compare the arms of the trial. It is hard to believe that no participant experienced nausea or vomiting. Other sources of bias • Low risk of bias Overall risk of bias • High Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Induction chemotherapy consisted of three cycles of cisplatin, at a dose of at least 80 mg/m 2 per cycle, or carboplatin, at a target area under the curve of at least 5 per cycle, combined with at least one other chemotherapy drug. Response was evaluated with CT scan after at least two cycles of induction chemotherapy and scored according to WHO criteria, but confirmation was not required. Eligibility was reassessed before random assignment. Only patients showing a response (complete, partial, or minor) to induction chemotherapy were eligible for random assignment. Surgery had to start within 6 weeks of random assignment. Postoperative radiotherapy consisting of 56 Gy in once-daily fractions of 2 Gy was recommended in cases of incomplete resection and had to start between the 4th and 10th postoperative week. • Chemotherapy, radiotherapy *Induction chemotherapy consisted of three cycles of cisplatin, at a dose of at least 80 mg/m 2 per cycle, or carboplatin, at a target area under the curve of at least 5 per cycle, combined with at least one other chemotherapy drug. Response was evaluated with CT scan after at least two cycles of induction chemotherapy and scored according to WHO criteria, but confirmation was not required. Eligibility was reassessed before random assignment. Only patients showing a response (complete, partial, or minor) to induction chemotherapy were eligible for random assignment. Radiotherapy had to start within 6 weeks of random assignment. The dosage administered to the primary tumour and involved mediastinum was 60–62.5 Gy and to the uninvolved mediastinum it was 40–46 Gy. The fractionation size was 1.95 – 2.05 Gy. A number of fractions were 30-32. The total treatment duration was 40-46 days.* **Outcome measures** • Mortality, all-cause • Dropout during treatment	