Evidence Tables

Citation: Arriagada,R.; Dunant,A.; Pignon,J.P.; Bergman,B.; Chabowski,M.; Grunenwald,D.; Kozlowski,M.; Le,Pechoux C.; Pirker,R.; Pinel,M.I.; Tarayre,M.; Le,Chevalier T. (2010). Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. Journal of Clinical Oncology, 28, 35-42. Updated analysis of Arriagada et al. (2004)

Design: RCT
Country: International

Aim: To assess the effect of platinum-based adjuvant chemotherapy compared to observation in patients with stage I-III completely resected NSCLC

Inclusion criteria
Patients
-pathologically proven stage I-III completely resected NSCLC
-aged 18-75
-no previous chemotherapy or radiotherapy
-no contraindications to chemotherapy
-no previous cancer apart from non-melanoma skin cancer or carcinoma in situ of the cervix

Exclusion criteria

Population
Chemotherapy: N = 932 (median age 59 years; 752 males; WHO PS 0/1/2: N = 505/355/72; TNM stage T1N0 / T2N0 / T1N1 / T2N1 / T3N0 / T3N1 / T1N2 / T2N2 / T3N2 / T4N0 / T4N1 / T4N2: N = 96/237/40/190/84/38/33/ 143/60/6/3/2; Surgery pneumonectomy/lobectomy/segmentectomy: N = 324/595/13; Histology squamous/ adeno/ large cell/mixed/other: N = 428/386/60/40/18. Ineligible: 17/932 patients)
Observation: N = 935 (median age 59 years; 750 males; WHO PS 0/1/2: N = 499/372/64; TNM stage T1N0 / T2N0 / T1N1 / T2N1 / T3N0 / T3N1 / T1N2 / T2N2 / T3N2 / T4N0 / T4N1 / T4N2: N = 87/261/40/182/73/37/24/ 160/54/6/8/3; Surgery pneumonectomy/lobectomy/segmentectomy: N = 324/603/8; Histology squamous/ adeno/ large cell/mixed/other: N = 444/368/62/41/20. Ineligible: N = 8/935)

Interventions
Chemotherapy: The following treatment options were possible:
Cisplatin:
- 80 mg/m^2 for 4 cycles delivered on days 1, 22, 43, and 64, or
- 100 mg/m^2 for 3 cycles delivered on days 1, 29, and 57, or
- 100 mg/m^2 for 4 cycles delivered on days 1, 29, 57, and 85, or
- 120 mg/m^2 for 3 cycles delivered on days 1, 29, and 71.

Drugs combined with cisplatin:
- Vindesine, 3 mg/m^2 per day delivered weekly from days 1 to 29 (frequency adapted according to blood count), then every 2 weeks after day 43 until last cisplatin dose.
- Vinblastine 4 mg/m^2 per day delivered weekly from days 1 to 29 (frequency adapted according to blood count), then every 2 weeks after day 43 until last cisplatin dose.
- Vinorelbine 30 mg/m^2 per day delivered weekly from day 1 to last cisplatin dose (frequency adapted according to blood count).
- Etoposide 100 mg/m^2 per day delivered on days 1-3 with each cisplatin dose.

Chemotherapy treatment was to start within 60 days of surgery and within 14 days of randomisation in the chemotherapy group.

Post-operative RT (PORT) consisted on ≤ 60 Gy delivered to the mediastinal nodes with conventional fractionation of the dose. PORT could not be administered, be administered to pathological N2 only, or be administered to pathological stages N1 and N2. When PORT was delivered it was administered after the completion of chemotherapy in the chemotherapy group and after randomisation in the observation group.

Outcomes
Survival, disease-free survival, second primary cancers, adverse events

Results
Chemotherapy and PORT delivery (data from Arriagada et al., 2004):
-49.3% chemotherapy patients were selected to receive a regimen combining 100 mg/m^2 cisplatin with etoposide for 3-4 cycles.
-73.8% chemotherapy patients received ≥ 240 mg/m^2 cisplatin.
-2.1% observation patients received chemotherapy.
-70.4% of the 284 chemotherapy patients assigned to receive PORT actually received PORT. 84.2% of the 288 observation patients assigned to receive PORT actually received PORT. Median total dose of PORT = 50 Gy.
-851/932 chemotherapy patients received chemotherapy and 7/851 chemotherapy patients died of toxic effects of chemotherapy (5 from bone marrow aplasia, 1 from renal failure and 1 from hyponatremia; 2/7 had received 120 mg/m^2 cisplatin, 4/7 had received 100 mg/m^2 cisplatin, and 1/7 had received 80 mg/m^2 cisplatin; Rathe of lethal toxic effect = 2.4% after 120 mg/m^2 cisplatin and .6% after 100 mg/m^2 cisplatin, p = .15).
-22.6% of the chemotherapy patients had ≥ one grade 4 toxic events (17.5% neutropenia, 2.6% thrombocytopenia, and 3.3% vomiting). Other grade 4 toxicities all ≤ 1%.
Survival:
- Hazard ratio (stratified by centre and adjusted for stage and surgery) = .91; 95% CI = .81-1.02; p = .1).
- Median survival = 54 and 45 months in the chemotherapy and observation groups, respectively.
- Interaction between follow up time periods (0-5 years v > 5 years) and chemotherapy was significant (p = .006): HR = .86 (95% CI .76-.97, p = .01) favouring chemotherapy for 0-5 years follow up; HR = 1.45 (95% CI 1.02-2.07, p = .04) favouring observation for > 5 years follow up.
- Chemotherapy did not interact with age, sex, performance status, type of surgery, tumour stage, N stage, cancer stage, histology, cisplatin dose, drug combined with cisplatin or RT (planned and delivered) (all ps ≥ .07).
- Death from non-lung cancer did not differ between the patient groups (HR = 1.34; 95% CI .99-1.81, p = .06.
-Death from non-lung cancer: Chemotherapy did not interact with age, performance status, initial dose of cisplatin or follow up period for this outcome.
Disease-free survival:
- 606 chemotherapy patients and 631 observation patients experienced disease progression (HR = .88; 95% CI = .78-.98; p = .02) favouring chemotherapy. .
- Interaction between follow up time periods (0-5 years v > 5 years) and chemotherapy was significant (p = .04): HR = .85 (95% CI .75-.95, p = .006) favouring chemotherapy for 0-5 years follow up; HR = 1.33 (95% CI .89-2, p = .16) for > 5 years follow up.
- Chemotherapy did not interact with disease stage.
Recurrence:
Local: The absolute benefit of chemotherapy at 5 and 8 years = 4.4% and 6.2%, respectively, HR = .74 (95% CI .61-.9, p = .002).
- Chemotherapy did not interact with follow up period.
Distant: The absolute benefit of chemotherapy at 5 and 8 years = 4.2% and 3.7%, respectively, HR = .84 (95% CI .72-.97, p = .02).
- Chemotherapy did not interact with follow up period.
-Non-brain metastasis: HR = .76 (95% CI .63-.9, p = .002).
-Brain metastasis: HR = 1.09 (95% CI .84-1.4, p = .53).
Second malignancies:
HR = .89 (95% CI .6-1.3, p = .54).
- Chemotherapy did not interact with follow up period.

General comments
The patients included in this trial were centrally randomised using a minimization procedure with stratification for participating centre, type of surgery, and pathological stage. Although no detail is reported about allocation concealment, it is likely that central randomisation has gone some way in ensuring allocation concealment. 1867 patients out of the projected 3300 patients were randomised. No blinding (e.g., of assessor of recurrence) appears to have been employed. The analyses included all randomised patients (whether eligible or not) and were conducted according to the intention-to-treat principle. The evidence provided by this RCT can therefore be considered of moderate quality.

References of Included Studies:
Arriagada,R.; Bergman,B.; Dunant,A.; Le,Chevalier T.; Pignon,J.P.; Vansteenkiste,J.; International Adjuvant Lung Cancer

Trial Collaborative Group. (2004). Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. The New England Journal of Medicine, 350, 351-360.

Citation: Auperin,A.; Le Chevalier,T.; Le Pechoux,C.; Pignon,J.P.; Tribodet,H.; Burdett,S.; Stewart,L.A.; Tierney,J.F.; Stephens,R.J.; Arriagada,R.; Higgins,J.P.; Johnson,D.H.; van Meerbeeck,J.; Parmar,M.K.B.; Souhami,R.L.; Bergman,B.; Dautzenberg,B.; Douillard,J.Y.; Dunant,A.; Endo,C.; Girling,D.J.; Imaizumi,M.; Kato,H.; Keller,S.M.; Kimura,H.; Knuuttila,A.; Kodama,K.; Komaki,R.; Kris,M.G.; Lad,T.; Mineo,T.; Park,J.H.; Piantadosi,S.; Pyrhonen,S.; Rosell,R.; Scagliotti,G.V.; Seymour,L.W.; Shepherd,F.A.; Spiro,S.G.; Strauss,G.M.; Sylvester,R.; Tada,H.; Tanaka,F.; Torri,V.; Wada,H.; Waller,D.; Xu,G.C. (2010). Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet, 375, 1267-77.

Design: Meta-analysis of individual patient data
Country: International

Aim: To assess the efficacy of surgery + adjuvant chemotherapy compared to surgery alone in patients with resectable NSCLC

Inclusion criteria
Published and unpublished randomised trials that were not confounded by additional therapeutic differences between the treatment groups, that started randomisation on or after Jan 1, 1965, and that aimed to include patients who had undergone a potentially curative resection and not received previous chemotherapy. These trials should have compared surgery plus adjuvant chemotherapy versus surgery alone.

Exclusion criteria
Trials using long-term alkylating agents for more than 1 year.

Population
26 studies (34 trial comparisons) with N = 4305 in the adjuvant chemotherapy + surgery group and N = 4142 in the surgery alone group:
Chemotherapy:
-Platinum-based chemotherapy without tegafur + uracil or tegafur alone: 18 trial comparisons
-Platinum-based chemotherapy with tegafur + uracil or tegafur alone: 8 trial comparisonss
-Cisplatin used as platinum agent: 25 trial comparisons
-Tegafur and uracil or tegafur alone used in combination with other agents: 1 trial comparison
-Tegafur and uracil or tegafur: 7 trial comparisons
Patients:
- Predominantly males
- Median age = 61 years (range 18–84)
- Predominance of good performance status
- Predominance of stage I-II adenocarcinoma or squamous cell tumours
- Median follow-up was 5.5 years (IQR 4.4–6.6).

Interventions
Adjuvant chemotherapy: Surgery + chemotherapy
Control: Surgery alone

Outcomes
Overall survival, time-to-recurrence (disease/progression-free survival)

Results
Survival (all patients): Hazard ratio (HR) = **.86 (95% CI .81-.92; p < .0001; I^2 = 4%, i.e., minimal heterogeneity**) favouring adjuvant chemotherapy. That is, the hazard of death is 14% lower in the adjuvant chemotherapy group than in the control group. At 5 years there was an absolute improvement of 4% (95% CI 3-6%) in the adjuvant chemotherapy group.
-The treatment effect did not vary significantly according to whether the trial comparisons were included in the 1995 meta-analysis or since, by accrual decade, or by geographical region.
-Treatment effect did not differ between trial comparisons that did and those that did not use tegafur and uracil or tegafur (p = .16)
-No patient subgroup (defined by age, sex, histology, performance status, or stage) were found to benefit significantly more or less from chemotherapy.

Survival (platinum + vinca alkaloid/etoposide trials: 9 trial comparisons, 2404 patients): HR = .94 (95% CI .84-1.05; ns; I^2 not reported).
Survival (platinum + vinorelbine trials: 4 trial comparisons, 1304 patients): HR = .82 (95% CI .7-.97; p = .021; I^2 not reported), favouring chemotherapy.
Survival (platinum + taxane trials: 1 trial comparison, 344 patients): HR = .77 (95% CI .57-1.05; ns).
Survival (other platinum regimens: 4 trial comparisons, 699 patients): HR = .9 (95% CI .72-1.13; ns; I^2 not reported).
Survival (platinum + vinca alkaloid + tegafur and uracil/tegafur trials: 8 trial comparisons, 1375 patients): HR = .79 (95% CI .67-.93; p = .005; I^2 not reported), favouring chemotherapy.
Survival (tegafur and uracil/tegafur + other agent trials: 1 trial comparison, 83 patients): HR = 1.79 (95% CI 1-3.2; ns).
Survival (tegafur and uracil/tegafur trials: 7 trial comparisons, 2390 patients): HR = .76 (95% CI .64-.9; p = .001; I^2 not reported).
Survival: Exploratory subgroup analyses:
- Platinum without tegafur and uracil or tegafur alone group: The effect of chemotherapy did not differ significantly between patients with good and poor performance status. However, a trend, consistent across trials, was noted of an increasing relative effect of chemotherapy with improving performance status (p = 0.002). The relative effect of chemotherapy did not differ significantly by other patient subgroups.
- Tegafur and uracil or tegafur alone group: The effect of chemotherapy did not differ significantly between patients with good and poor performance status. However, a trend, inconsistent across trials, was noted of an increasing relative effect of chemotherapy with worsening performance status (p = 0.02). The relative effect of chemotherapy did not differ significantly by other patient subgroups according to age, gender, histology, or stage.
Recurrence-free survival (18 trial comparisons; 5379 patients): HR = **.83 (95% CI .77-.9; p < .0001; I^2 not reported**) favouring adjuvant chemotherapy. Exclusion of the trial comparisons (N = 4) that included tegafur and uracil or tegafur alone gave similar results.
Time to loco-regional recurrence (16 trial comparisons; 5226 patients): HR = **.75 (95% CI .66-.85; p < .0001; I^2 not reported**) favouring adjuvant chemotherapy. Exclusion of the trial comparisons (N = 4) that included tegafur and uracil or tegafur alone gave similar results.
Time to distant recurrence (16 trial comparisons; 5224 patients): HR = **.8 (95% CI .72-.89; p = .0007; I^2 not reported**) favouring adjuvant chemotherapy. Exclusion of the trial comparisons (N = 4) that included tegafur and uracil or tegafur alone gave similar results.

General comments
The authors of this systematic review appear to have conducted a thorough search for both published and unpublished source data with extensive data integrity checking. However, the quality of the studies included in this meta-analysis were not assessed and, although the analyses were performed according to the intention to treat principle, the I^2 value is not reported for some of the analyses making it difficult to fully evaluate between-study heterogeneity, and consequently the validity of the observed results. These results must therefore be interpreted with caution. The evidence provided by this meta-analysis can therefore only be considered of moderate quality.

References of Included Studies (for systematic review):

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chemoimmunotherapy of resected non-small cell lung cancer with IL2 and LAK cells. *Lung Cancer* 1991; **7** (suppl)**:** 133.
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Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 2008; **26:** 5043–51.
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Citation: Belani, C. P., Wang, W., Johnson, D. H., Wagner, H., Schiller, J., Veeder, M. et al. (2005). Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small-cell lung cancer. *Journal of clinical oncology, 23,* 3760-3767.

Design: RCT
Country: USA

Aim: To assess the efficacy of hyperfractionated accelerated radiotherapy (HART) compared to standard once-daily thoracic radiotherapy (RT) after induction chemotherapy in patients with unresectable stage IIIA or IIIB NSCLC.

Inclusion criteria
Patients with
-histologically/cytologically confirmed stage IIIa or IIIB unresectable previously untreated NSCLC
-age > 18 years
-ECOG performance status (PS) ≤ 1
-bidimensional measurable disease

-no pleural effusion on chest x-ray, no collapse of an entire lung, no prior malignancies in preceding 5 years (except non-melanoma skin cancer or carcinoma in situ of the cervix, no active peptic ulcer/esophageal reflux/ hiatal hernia
-consent to abstain from smoking during HART/RT

Exclusion criteria
Patients with tumour location where 100% of the cardiac volume would not receive more than 45 Gy, or where 50% of cardiac volume would receive no more than 50 Gy.

Population
Hyperfractionated accelerated radiotherapy (HART): N = 56 (median age 65.7 years; 35 males; ECOG PS 0/1: N = 26/30; T stage 1/2/3/4: N = 4/14/10/27; N stage 0/1/2/3/4/X: N = 9/2/29/15/1/0).
Once-daily RT (sRT): N = 56 (median age 63.4 years; 33 males; ECOG PS 0/1: N = 19/37; T stage 1/2/3/4: N = 9/16/4/26; N stage 0/1/2/3/4/X: N = 4/0/33/18/0/1).

Interventions
All patients: Induction chemotherapy consisted of 2 3-weekly cycles of carboplatin area under the time-concentration curve 6 mg/mL/min on days 1 and 22 + paclitaxel 225 mg/m^2 on day 1. Patients without metastatic progression were randomised to one of the following two groups:
HART: 57.6 Gy/36 fractions delivered 3 times a day (am, early pm, late pm; with min 4-hour interval between fractions) 5 days a week.
sRT: 64 Gy/32 fractions of 2 Gy delivered once daily 5 days per week
Radiotherapy not allowed in either group.
HART/RT began between days 43 and 50.

Outcomes
Survival, toxicity.

Results
RT delivery:
-Median time to RT completion = 17 (range 17-33) and 51 (range 27-76) elapsed days for the HART and sRT patients, respectively.
-RT completion rates = 54/56 and 53/56 for the HART and sRT patients, respectively.
Toxicity:
-Radiotherapy: Acute events of grade 3-4 in the HART and sRT patients respectively: Esophagitis (N = 14 and 9), pulmonary (N = 0 and 6), skin (N = 0 and 1). No late events were observed.
-Chemotherapy: Acute events of grade 3-4 in the HART and RT patients respectively: Leukopenia (N = 1 and 4), neutropenia (N = 2 and 1), nausea (N = 1 and 2), neurotoxicity (N = 0 and 6), fatigue (N = 0 and 2). Incidence of grade ≥ 3 toxicities = 18/56 and 25/56 in the HART and sRT patients, respectively (ns). There were no toxic deaths.
Survival and response:
-The 1-, 2- and 3-year survival rates = 59 (95% CI 46-72)%, 44 (95% CI 31-57)% and 24%, respectively, in the HART group and 54 (95% CI 40-67)%, 34 (95% CI 22-46)% and 18%, respectively, in the sRT group. Median survival time = 20.3 (95% CI 11.6-25.5) months in the HART group and 14.9 (95% CI 10-23.1) months in the sRT group. Overall survival did not differ between the groups.
-Median time to progression = 8.2 months in the HART group and 9.3 months in the sRT group (ns).
- Best overall response rates = 25 and 22% in the HART and sRT groups, respectively (ns).

General comments
Although patients in this trial were randomised, it is unclear which method of randomisation was used and whether allocation concealment was employed. In addition, progression and toxicity appears to have been assessed without blinding and only 141 out of the estimated target 338 patients were enrolled before the trial closed. Collectively, these different issues make it difficult to know what do make of the results because of the obvious potential for bias(es) combined with low power. The evidence provided by this RCT can therefore only be considered to be of low quality.

References of Included Studies: NA

Citation: Belderbos, J., Uitterhoeve, L., van, Z. N., Belderbos, H., Rodrigus, P., van, d., V et al. (2007). Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). *European journal of cancer (Oxford, England : 1990), 43,* 114-121.

Design: RCT
Country: Europe

Aim: To compare concurrent chemoradiation (C-ChRT) with sequential chemoradiotherapy (S-ChRT) in patients with inoperable stage T1-4N0-3 (excluding N3 disease based on supra-clavicular nodes) NSCLC

Inclusion criteria
Patients with inoperable stage T1-4N0-3 (excluding N3 disease based on supra-clavicular nodes) NSCLC

Exclusion criteria

Population
S-ChRT: N = 78 (median age 64 years; 78% males; WHO PS 0/1: 42%/58%; Clinical stage I/II/IIIA/IIIB/unknown: 3% / 4% /45% / 47% / 1%; delay between diagnosis and randomisation ≤30days / ≤56 days / > 56 days: 41% / 42% / 17%).
C-ChRT N = 80 (median age 62 years; 74% males; WHO PS 0/1: 44% / 56%; Clinical stage I/II/IIIA/IIIB/unknown: 1% / 5% / 30% / 64% / 0%; delay between diagnosis and randomisation ≤30days / ≤56 days / > 56 days: 55% / 29% / 16%).

Interventions
S-ChRT: 2 cycles of gemcitabine 1250 mg/m^2 on days 1 and 8 + cisplatin 75 mg/m^2 on day 2 with a 3 week interval followed by radiotherapy (RT) with a total dose = 66 Gy (24 fractions of 2.75 Gy over 32 days)
C-ChRT: Daily cisplatin 6 mg/m^2 1-2 hours before each RT fraction concurrent with RT with a total dose = 66 Gy (24 fractions of 2.75 Gy over 32 days)

Outcomes
Survival, toxicity

Results
Treatment delivery and toxicity (data from the patients who started protocol treatment):
-76/78 and 66/80 patients in the S- and C-ChRT groups, respectively, started treatment
-64/78 and 54/80 patients in the S- and C-ChRT groups, respectively, received full-dose chemotherapy
-74/78 and 64/80 patients in the S- and C-ChRT groups, respectively, received full-dose RT
-Thrombocytopenia G3/4: 7% S-ChRT patients and 0% C-ChRT patients, respectively.
-Leucocytopenia G3/4: 7% S-ChRT patients and 3% C-ChRT patients, respectively.
-Granulocytopenia G3/4: 21% S-ChRT patients and 2% C-ChRT patients, respectively.
-Nausea G3: 7% S-ChRT patients and 6% C-ChRT patients, respectively.
-Esophagitis G3/4: 5% S-ChRT patients and 17% C-ChRT patients, respectively.
-Shortness of breath G3/4: 8% S-ChRT patients and 9% C-ChRT patients, respectively.
-Lethargy G3: 5% S-ChRT patients and 6% C-ChRT patients, respectively.
-Infection G3: 5% S-ChRT patients and 5% C-ChRT patients, respectively.
-Vomiting G3: 4% S-ChRT patients and 6% C-ChRT patients, respectively.
-Late toxicity: Lung G3/4: 14% S-ChRT patients and 18% C-ChRT patients, respectively.
-Late toxicity: Esophageal symptoms G3: 4% S-ChRT patients and 5% C-ChRT patients, respectively.
-Late toxicity: Other G3: 8% S-ChRT patients and 15% C-ChRT patients, respectively.
-1 patient in each group died from lung haemorrhage, possibly treatment-related.
Survival:
1-, 2-, and 3-year survival rates = 69%, 33.6%, and 21.6%, respectively in the S-ChRT group and = 55.9%, 38.5%, and 29.2% in the C-ChRT group. Median survival = 16.2 and 16.5 months in the S-ChRTgroup and C-ChRT group, respectively. Overall survival did not differ between the groups (hazard ratio (HR) = 1.06; 95% CI .74-1.52, ns).
Progression-free survival:
1-year progression-free survival rates = 44.5% and 36.3%, respectively, in the S-ChRT group and the C-ChRT group. Median progression-free survival = 10.8 and 8.5 months in the S-ChRTgroup and C-ChRT group, respectively. Progression-free survival did not differ between the groups (HR = .79; 95% CI .56-1.1, ns).
Response:
53/78 S-ChRT and 40/80 C-ChRT patients achieved a complete or partial response. These response rates did not statistically differ when considering all patients who started treatment (p = .29).
At 39 months follow-up 43% S-ChRT and 46% C-ChRT patients had experienced loco-regional tumour progression and 50% of bnoth S-ChRT and C-ChRT patients had experienced distant metastasis.

General comments
The patients included in this trial were randomised with stratification for performance status, TNM stage and institution.

No additional detail was reported about the randomisation method or whether allocation concealment was employed. Although the main analyses were conducted according to the intention-to-treat principle, no statistical analyses assessing whether the treatment groups were balanced on the baseline characteristics were reported, and it would appear that there may have been significantly more patients with stage IIIB in the C-ChRT group than in the S-ChRT group at baseline. The evidence provided by this RCT can therefore be considered of low quality.

References of Included Studies: NA

Citation: Berghmans,T.; Paesmans,M.; Meert,A.P.; Mascaux,C.; Lothaire,P.; Lafitte,J.J.; Sculier,J.P. (2005). Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. Lung Cancer, 49, 13-23

Design: Meta-analysis
Country: International

Aim: To assess the efficacy of adjuvant chemotherapy in patients with resectable NSCLC
NOTE: This meta-analysis also assess the efficacy of neo-adjuvant chemotherapy in patients with resectable NSCLC. However, 5/6 of the included studies in this comparison overlap with those included in the Cochrane Review by Burdett, S, Stewart, L., & Rydzewska, L. ((2007). Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. Cochrane Database of Systematic Reviews: Reviews 3). The final study (pass et al., 1992) included by Berghmans et al. was excluded by Burdett et al. due to radiotherapy administration in only one of the study arms thereby confounding the results. In addition, the Burditt review has included two further trials (published in 2005) not included by Berghmans et al. The analyses pertaining to neo-adjuvant chemotherapy reported by Berghmans et al. will therefore not be reported here.

Inclusion criteria
Prospective RCTs assessing chemotherapy given after surgery.

Exclusion criteria

Population
19 RCTs with 7644 stage I-III patients

Interventions
Adjuvant chemotherapy: Surgery + combinations of cisplatin, adriamycin, vindesin, cyclophosphamide, vincristin, vinblastin, vinorelbin and tegafur + uracil.
Control: Surgery + radiotherapy/bacillus Calmette-Guerin + levamisole/no additional intervention.

Patients with late-stage disease/incomplete resection were offered radiotherapy.

Outcomes
Survival

Results
Survival (all patients):
Hazard ratio = **.84 (95% CI .78-.89**) favouring adjuvant chemotherapy. That is, adjuvant chemotherapy is associated with an overall 16% reduction in the risk of death relative to the control condition (no significant heterogeneity evident).
Survival (platinum trials; 13 studies):
Hazard ratio = **.86 (95% CI .8-.92**) favouring adjuvant chemotherapy. That is, platinum-based adjuvant chemotherapy is associated with an overall 14% reduction in the risk of death relative to the control condition (no significant heterogeneity evident).
Survival (tegafur+uracil trials; 6 studies):
Hazard ratio = **.72 (95% CI .61-.85**) favouring adjuvant chemotherapy. That is, cisplatin adjuvant chemotherapy is associated with an overall 28% reduction in the risk of death relative to the control condition (no significant heterogeneity evident).
Survival (without post-operative radiotherapy; 13 studies):
Hazard ratio = **.81 (95% CI .73-.89**) favouring adjuvant chemotherapy. That is, adjuvant chemotherapy is associated with an overall 19% reduction in the risk of death relative to the control condition (no significant heterogeneity evident).
Survival (with post-operative radiotherapy; 4 studies):
Hazard ratio = **.86 (95% CI .77-.97**) favouring adjuvant chemotherapy. That is, adjuvant chemotherapy is associated with

an overall 14% reduction in the risk of death relative to the control condition (no significant heterogeneity evident).

General comments

The literature search strategy was not described in detail and no attempts to identify unpublished reports were apparently made. In addition, the studies included in this systematic review were generally not of high quality, and little detail about the patients was reported. Taken together these different limitations introduce the potential for different types of bias and as a consequence, the results must be interpreted with caution. The evidence provided by this meta-analysis can therefore only be considered of moderate quality.

References of Included Studies (for systematic review):

-Arriagada, R., Bergman, B., Dunant, A., Le, C. T., Pignon, J. P., Vansteenkiste, J. et al. (2004). Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *The New England journal of medicine, 350,* 351-360.

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-Scagliotti, G. V., Fossati, R., Torri, V., Crinò, L., Giaccone, G., Silvano, G. et al. (2003). Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer. *Journal of the National Cancer Institute., 95,* 1453-1461.

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Citation: Bria,E.; Gralla,R.J.; Raftopoulos,H.; Cuppone,F.; Milella,M.; Sperduti,I.; Carlini,P.; Terzoli,E.; Cognetti,F.; Giannarelli,D. (2009) Magnitude of benefit of adjuvant chemotherapy for non-small cell lung cancer: meta-analysis of randomized clinical trials Lung Cancer, 63, 50-57.

Design: Meta-analysis
Country: International

Aim: To assess the efficacy of adjuvant chemotherapy in previously untreated patients with resectable NSCLC

Inclusion criteria
Meta-analyses or prospective RCTs assessing chemotherapy given after surgery with or without post-operative radiotherapy that have either been published in peer-reviewed journals or presented at ASCO, ECCO, ESMO or IASLC conferences.

Exclusion criteria

Population
13 studies with 7334 stage I-III patients (N = 3671 patients receiving adjuvant chemotherapy + surgery and N = 3663 receiving surgery without chemotherapy)

Interventions
Adjuvant chemotherapy: Surgery + chemotherapy
Control: Surgery ± post-operative radiotherapy.

Outcomes
Overall survival, time-to-recurrence (disease/progression-free survival)

Results
Survival (7408 patients):
Relative risk (RR) = **.91 (95% CI .85-.97; p = .01**) favouring adjuvant chemotherapy. That is, the risk of death is 9% lower in the adjuvant chemotherapy group than in the control group. Number needed to treat (NNT) = 30. However, there was significant heterogeneity between the studies (p = .048).
When sub-group analyses were performed on the basis of the size of the trials, the inclusion/exclusion of carboplatin trials and/or abstracts or older trials and trials with radiotherapy, heterogeneity was still present in the majority of analyses with the exception of:
- Large (≥ 100 patients) trials (5002 patients): RR= **.91 (95% CI .86-.96; p = .001**) favouring adjuvant chemotherapy. That is, the risk of death is 9% lower in the adjuvant chemotherapy group than in the control group. NNT = 30.
- Stage I patients (1888 patients): RR= **.88 (95% CI .79-.98; p = .02**) favouring adjuvant chemotherapy. That is, the risk of death is 12% lower in the adjuvant chemotherapy group than in the control group. NNT = 26.
Disease-free survival (5849 patients):
Relative risk (RR) = **.87 (95% CI .79-.94; p = .0006**) favouring adjuvant chemotherapy. That is, the risk of recurrence is 13% lower in the adjuvant chemotherapy group than in the control group. NNT = 26. However, there was significant heterogeneity between the studies (p = .01).
When sub-group analyses were performed on the basis of the size of the trials, the inclusion/exclusion of carboplatin trials and/or abstracts or older trials, heterogeneity was still present in the majority of analyses with the exception of:
- Large trials (5002 patients): RR= **.88 (95% CI .84-.92; p < .0001**) favouring adjuvant chemotherapy. That is, the risk of recurrence is 12% lower in the adjuvant chemotherapy group than in the control group. NNT = 21.

Quality of life (QoL) data from the Winton et al. study published by Bezjak et al. (2008);
-European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30)
-Completed at baseline (within 14 days before random assignment by 186/242 patients in the chemotherapy group and 172/240 observation patients), at weeks 5 and 9 in the chemotherapy group and at 3, 6, 9, and 12 months after

randomisation in both study arms as well as at subsequent 6-monthly clinic appointments. The completion rate ranges between 60-80% in assessments after baseline and these did not differ significantly between the groups.
-Baseline: No differences in QoL were observed between the groups.
-**Baseline-3 months: A significantly higher proportion of observation patients experienced improved global, physical, role, cognitive, and social functioning QoL compared to the chemotherapy patients, who reported worsened fatigue, appetite hair loss, nausea and vomiting.**
-9 months and beyond: No differences were observed between the groups in global QoL, or in physical, emotional, role, cognitive, and social functioning QoL. However, chemotherapy patients had better scores in nausea symptoms, but worse scores for numbness, pins and needles, and hearing loss compared to the observation group. Numbness of the fingers/toes and pins/needles sensation persisted, with detectable clinically significant differences (change scores of 10 to 20 points) up to 30 months.

General comments
Although the results of the literature search are not fully reported and potential publication bias is not addressed, the search terms are comprehensive and the inclusion of conference abstracts may serve to reduce the risk of a potential publication bias. However, the quality of the studies included in this meta-analysis were not assessed and limited detail of the patients was reported both of which may in part explain (some of) the heterogeneity observed. Consequently, the results must be interpreted with caution. The evidence provided by this meta-analysis can therefore only be considered of moderate quality.

References of Included Studies (for systematic review):

-Arriagada, R., Bergman, B., Dunant, A., Le, C. T., Pignon, J. P., Vansteenkiste, J. et al. (2004). Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *The New England journal of medicine, 350,* 351-360.
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-Xu, G., Rong, T., & Lin, P. (2000). Adjuvant chemotherapy following radical surgery for non-small-cell lung cancer: A randomized study on 70 patients. Chinese Medical Journal (Engl), 113, 617-20

Citation: Burdett, S, Stewart, L., & Rydzewska, L. (2007). Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. Cochrane Database of Systematic Reviews: Reviews 3.

Design: Cochrane systematic review
Country: International

Aim: To assess the efficacy of chemotherapy given before surgery in patients with NSCLC

Inclusion criteria
RCTs comparing surgery alone to chemotherapy followed by surgery in adult patients with NSCLC who had not previously received chemotherapy or had any prior malignancy.

Exclusion criteria

Population
7 RCTs with 988 (N = 493 in neoadjuvant + surgery group and N = 495 in surgery group) patients with all reporting overall survival and 3/7 trials (with 457 patients; N = 229 in neoadjuvant + surgery group and N = 228 in surgery group) reporting disease-free survival

Interventions
Chemotherapy + surgery:
-Neo-adjuvant: A variety of platinum-based chemotherapy-based regimens.
-Post-surgery: Patients in 2 RCTs received chemotherapy on the neo-adjuvant arm only; patients in 3 RCTs received post-operative radiotherapy on both arms; patients in 1 RCT received post-operative chemotherapy on the neo-adjuvant arm only and post-operative radiotherapy on both arms; 1 RCT reported no post-operative treatment.

The samples in all the studies consisted of patients with complete or incomplete resection, and 4 RCTs included patients with stage I-III disease whereas the remaining 3 RCTs only included stage III patients.

Outcomes
Overall and disease-free survival

Results
Overall Survival:
Hazard ratio = **0.82 (95% CI 0.69-0.97; p = .022**) favouring pre-operative chemotherapy. That is, pre-operative chemotherapy is associated with an overall 18% reduction in the risk of death relative to surgery alone, which is equivalent to an absolute improvement of 6% at 5 years, increasing overall survival from 14% to 20% (no heterogeneity evident).
Disease-free survival:
Hazard ratio = **0.78 (95%CI 0.52-0.99**) favouring pre-operative chemotherapy. That is, pre-operative chemotherapy is associated with an overall 22% reduction in the risk of progression of disease relative to surgery alone. *However, there was heterogeneity between the trials included in this analysis.*
Overall survival by stage of disease:
There appeared to be no difference in treatment effect between trials that included only stage III patients and those recruiting stage I-III patients (p = .57). 34%, 26% and 39% of the patients in 3/4 trials recruiting patients with stage I-III disease were stage I, II, and III, respectively.

General comments
Although the literature search appears to be thorough, the 7 RCTs included in this systematic review were not of high quality and an additional 5 studies that met inclusion criteria were excluded due to inadequate reporting of the outcome data. Consequently, the results must be interpreted with caution, and this point is further underscored by the presence of unexplained heterogeneity in one of the meta-analyses. The evidence provided by this Cochrane Review can therefore only be considered of moderate quality.

References of Included Studies (for systematic review):
-Dautzenberg B, Benichou J, Allard P, Lebeau B, Coetmeur D, Brechot J-M, et al.Failure of the perioperative PCV neoadjuvant polychemotherapy in resectable bronchogenic non-small cell carcinoma. *Cancer* 1990; **65**: 2435–41.

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-Pisters K, Vallieres E, Bunn P, Crowley J, Ginsberg R, Ellis P, et al.S9900: A phase III trial of surgery alone or surgery plus pre-operative (pre-op) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Preliminary results. Proceedings of the American Society of Clinical Oncology. 2005; Vol. 24: LBA7012.

Citation: Butts,C.A.; Ding,K.; Seymour,L.; Twumasi-Ankrah,P.; Graham,B.; Gandara,D.; Johnson,D.H.; Kesler,K.A.; Green,M.; Vincent,M.; Cormier,Y.; Goss,G.; Findlay,B.; Johnston,M.; Tsao,M.S.; Shepherd,F.A. (2010). Randomized Phase III Trial of Vinorelbine Plus Cisplatin Compared With Observation in Completely Resected Stage IB and II Non-Small-Cell Lung Cancer: Updated Survival Analysis of JBR-10. Journal of Clinical Oncology, 28, 29-34. (Updated analysis of Winton et al., 2005)

Design: RCT
Country: USA & Canada

Aim: To assess the effectiveness of adjuvant vinorelbine + cisplatin in patients with stage IB-II resected NSCLC

Inclusion criteria
-completely resected T2N0, T1N1, or T2N1 NSCLC
-age ≥ 18 years
-acceptable baseline characteristics
-ECOG performance status = 0 or 1
Intraoperative mediastinal lymph node resection or biopsy of nodes ≥ 1.5 cm was mandatory.

Exclusion criteria
-incomplete preoperative or intraoperative staging
-incomplete resection
-wedge or segmental resection
-involvement of tracheobronchialangle nodes (station 10) or more central mediastinal nodes
-mixed histological features,
-T3 tumour
-diffuse lobar or multifocal bronchioalveolar carcinoma
-history of breast cancer, renal-cell carcinoma, melanoma, or other cancers treated within the previous 5 years
-clinically significant cardiac dysfunction
-active infectiojn
-neurologic or psychiatric disorders

Population
Chemotherapy: N = 242 (median age 61 years; 66% males; Stage IB/IIA/IIB: 46% / 16% / 38%; Pathological tumour stage 1/2: 16% /84 %; Nodal status 0/1: 46% / 54%; Histology squamous/adeno/undifferentiated/mixed: 37% / 53% / 8% / 2%; ECOG PS 0/1: 50% / 50%; *ras* status mutation present/wild type/unknown: 24% / 68% / 8%; Extent of resection lobectomy/bilobectomy/pneumonectomy: 66% / 9% / 25%)
Observation: N = 240 (median age 61 years; 64% males; Stage IB/IIA/IIB: 45% / 13% / 42%; Pathological tumour stage 1/2: 13% /87 %; Nodal status 0/1: 45% / 55%; Histology squamous/adeno/undifferentiated/mixed: 38% / 53% / 7% / 2%; ECOG PS 0/1: 49% / 51%; *ras* status mutation present/wild type/unknown: 24% / 70% / 6%; Extent of resection

lobectomy/bilobectomy/pneumonectomy: 71% / 7% / 22%)

Interventions
Chemotherapy: Four 4-weekly cycles of cisplatin 50 mg/m^2 on days 1 and 8 + weekly vinorelbine 25 mg/m^2 for 16 weeks.

All patients received ondansetron, often with a corticosteroid, and chemotherapy was adjusted for toxicity according to protocol guidelines. Patients were randomised within 6 weeks of surgery and treatment started within 2 days of randomisation.

Outcomes
Survival, recurrence-free survival, toxicity

Results *Median follow up = 9.3 years, 15 observation and 18 chemotherapy patients were lost to follow up*
Chemotherapy delivery (data from Winton et al., 2005):
-110, 133, 156 and 204 patients completed cycles 4, 3, 2 and 1, respectively. 27 patients completed day 1 of cycle 1 and 11 patients in the chemotherapy group were never treated. The median number of cycles = 3.
-77% of the patients had ≥ 1 dose reduction or omission and 55% had ≥ 1 dose delay.
Toxicity (data from Winton et al., 2005):
-Rates of grade 3/4 toxicity: Fatigue (15%), anorexia (10%), alopecia (0%), local toxicity (3%), diarrhea (< 1%), nausea (10%), vomiting (7%), constipation (3%), infection (1%), febrile neutropenia (6%), hearing loss (2%), sensory neuropathy (2%), motor neuropathy (3%), dyspnea (4%), thrombocytopenia (1%), anaemia (7%), neutropenia (73%), ALT/bilirubin/creatinine elevation (all < 1%).
-2 patients died from treatment-related toxicity
Survival:
-Overall survival: Hazard ratio (HR) = .78; 95% CI = .61-.99; p = .04). Median survival = 94 months in the chemotherapy group and 73 months in the observation group (data from Winton et al., 2005)**.** 5-year survival = 67% in the chemotherapy group and 56% in the observation patients.
-The beneficial effect of chemotherapy (HR = .79; 95% CI = .62-1; p = .05) was not significant when the analysis (multivariate) adjusted for age, gender, performance status, extent of resection, and histologic features.
- Disease stage and chemotherapy were not found to interact.
- ras mutation status was not found to interact with chemotherapy for either overall or disease-specific survival.
Disease-specific survival:
-HR = .73; 95% CI = .55-.97; p = .03) favouring chemotherapy (adjusted HR = .73; 95% CI .55-.96, p = .03).
-The observation patients had a significantly increased risk of dying from lung cancer compared to the chemotherapy patients (p = .02). The risk of death from other causes did not differ between the two patient groups.

General comments some analyses not reported due to data mining
The patients included in this trial were randomised with stratification for nodal status and *ras* mutation status. No details are reported about whether central randomisation and/or potential allocation concealment were employed. It also appears that no level of blinding (e.g., of assessor of recurrence) was employed. The trial was well-powered and the analyses were conducted on an intention-to-treat basis. Some analyses are not reported because they appear to be subject to data mining with no correction for multiple analyses. Overall, the evidence included from this RCT can therefore be considered to be of moderate quality.

References of Included Studies:
Winton, T., Livingston, R., Johnson, D., Rigas, J., Johnston, M., Butts, C., Cormier, Y., Goss, G., Inculet, R., Vallieres, E., Fry, W., Bethune, D., Ayoub, J., Ding, K., Seymour, L., Graham, B., Tsao, M. S., Gandara, D., Kesler, K., Demmy, T., Shepherd, F., National Cancer Institute of Canada Clinical Trials Group & National Cancer Institute of the United States Intergroup JBR. (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *The New England journal of medicine,* 352: 2589-2597.

Citation: Douillard,J.Y.; Rosell,R.; De Lena,M.; Carpagnano,F.; Ramlau,R.; Gonzales-Larriba,J.L.; Grodzki,T.; Pereira,J.R.; Le Groumellec,A.; Lorusso,V.; Clary,C.; Torres,A.J.; Dahabreh,J.; Souquet,P.J.; Astudillo,J.; Fournel,P.; rtal-Cortes,A.; Jassem,J.; Koubkova,L.; His,P.; Riggi,M.; Hurteloup,P. (2006). Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncology, 7, 719-727.

Design: RCT

Country: International

Aim: To assess the effect of adjuvant vinorelbine + cisplatin chemotherapy compared to observation in patients with stage IB-IIIA completely resected NSCLC

Inclusion criteria
-Histologically proven stage I (only T2N0)-IIIA completely resected NSCLC (apart from bronchoalveolar carcinoma)
-aged 18-75
-WHO performance status 0-2
-adequate biological functions

Exclusion criteria
-History of concurrent malignant disease (apart from adequately treated non-melanoma skin cancer or in situ cervical cancer) or other previous primary tumours

Population
Chemotherapy: N = 407 (median age 59 years; 346 males; WHO PS 0/1/2/missing: N = 196/192/14/5; Post-operative stage I/II/IIIA/IIIB-IV/missing: N = 146/89/166/2/4; Nodal status N0/N1/N2/missing: N = 179/107/118/ 3; Surgery pneumonectomy/lobectomy/other/missing: N = 155/233/16/3; Histology squamous/non-squamous /mixed squamous and non-squamous/missing: N = 240/ 163/1/3)
Observation: N = 433 (median age 59 years; 375 males; WHO PS 0/1/2/missing: N = 225/189/14/5; Post-operative stage I/II/IIIA/IIIB-IV/missing: N = 155/114/159/2/3; Nodal status N0/N1/N2/missing: N = 188/136/106/ 3; Surgery pneumonectomy/lobectomy/other/ missing: N = 155/253/23/2; Histology squamous/non-squamous/ mixed squamous and non-squamous/missing: N = 253/175/3/2)

The biological variables, medical and surgical history, tobacco and alcohol consumption, and clinical characteristics at baseline did not differ between the chemotherapy and observation groups.

Interventions
Chemotherapy: Four 4-weekly cycles of vinorelbine 30 mg/m^2 on days 1, 8, 15, and 22, and 100 mg/m^2 cisplatin on day 1. Post-operative RT (PORT) was optional, but eventually recommended for node-positive disease. PORT consisted of 45-60 Gy in 2 Gy fractions, 5 times a week. When PORT was delivered it was administered within 2 weeks after the completion of chemotherapy in the chemotherapy group and within 2 weeks after randomisation in the observation group.

Outcomes
Survival, disease-free survival, adverse events

Results
Chemotherapy delivery in chemotherapy group:
-368 patients received vinorelbine and 267 of these also received concurrent cisplatin. 141 and 233 of these patients received > 66% of the total planned dose of vinorelbine and cisplatin, respectively, and 202 patients completed the planned 4 cycles.
-Chemotherapy compliance was not statistically significantly associated with type of surgery.
-39 patients did not start chemotherapy and a further 9 patients were ineligible.
Toxicity:
The 5 most frequent grade 3-4 toxicities in the chemotherapy group were: Neutropenia (N = 308), asthenia (N = 97), nausea & vomiting (N = 95), anorexia (N = 52), and anaemia (N = 50). No type of grade 3-4 toxicities was experienced by > 10 patients (per toxicity) in the observation group (total number of grade 3-4 toxicities in observation group = 26).
-Chemotherapy-related deaths: N = 7.
PORT delivery:
N = 88 and 144 in the chemotherapy and observation groups, respectively, received PORT (p = .0002).
Survival:
Median survival = 65.7 (95% CI 47.9-88.5) months in the chemotherapy group and 43.7 (95% CI 35.7-52.3) months in the observation group **(hazard ratio (HR) = .8; 95% CI = .66-.96; p < .017).** The absolute survival benefit for the chemotherapy patients = 2.8% at 1 year, 4.7% at 2 years, 8.6% at 5 years, and 8.4% at 7 years. **Multivariate analysis indicated that age < 55 years (HR = .76; 95% CI .62-.93), disease stage ≤ II (HR = .63; 95% CI .51-.77), and no lymph node involvement (HR = .6; 95% CI .48-.74) to be significantly associated with better survival (in addition to treatment group).**
Disease-free survival:

Median disease-free survival = 36.3 (95% CI 28-52.1) months in the chemotherapy group and 20.7 (95% CI 16.1-28.6) months in the observation group **(HR = .76; 95% CI = .64-.91; p < .002).** The absolute survival benefit for the chemotherapy patients = 9% at 6 months, 9.5% at 1 years, 9.6% at 2 years, 8.7% at 5 years and 5.5% at 7 years.
Relapse
-Local relapse: N = 49 and 76 in the chemotherapy and observation groups, respectively (p = .025).
-Distant relapse: N = 101 and 122 in the chemotherapy and observation groups, respectively (p = .27).
-Most common site of relapse = lung in both groups: N = 91 and 123 in the chemotherapy and observation groups, respectively (p = .004).
-Bone metastasis: N = 15 and 46 in the chemotherapy and observation groups, respectively (p = .0001).
-Brain metastasis: N = 53 and 43 in the chemotherapy and observation groups, respectively (p = .16).
-Brain as only site of relapse: N = 38 and 34 in the chemotherapy and observation groups, respectively.

General comments
The patients included in this trial were centrally randomised with stratification for participating centre, stage, and histology. However, although the patients were centrally randomised, allocation concealment was not employed. 840 patients out of the projected 800 patients were randomised. This trial was open label trial, and no level of blinding (e.g., of assessor of recurrence) was employed. The analyses were conducted according to the intention-to-treat principle. The corresponding author had the final responsibility for the decision to submit this trial for publication, however it appears that the study sponsor/funding body participated in the data collection, data analysis and patient monitoring. Although the trial is well-powered and the analyses were conducted on an intention-to-treat basis, the absence of allocation concealment and blinding taken together with the apparent involvement of the funding source in the data collection, analysis and patient monitoring introduce the potential for a number of biases that collectively serve to undermine the integrity of the results. The evidence provided by this RCT can therefore only be considered to be of low quality.

References of Included Studies: N/A

Citation: Douillard,J.Y.; Tribodet,H.; Aubert,D.; Shepherd,F.A.; Rosell,R.; Ding,K.Y.; Veillard,A.S.; Seymour,L.; Le Chevalier,T.; Spiro,S.; Stephens,R.; Pignon,J.P. (2010). Adjuvant Cisplatin and Vinorelbine for Completely Resected Non-small Cell Lung Cancer Subgroup Analysis of the Lung Adjuvant Cisplatin Evaluation. Journal of Thoracic Oncology, 5, 220-228.

Design: Subgroup analyses of a meta-analysis (conducted by Pignon et al., 2008) of individual patient data from the five largest randomised trials comparing cisplatin-based adjuvant chemotherapy to observation in completely resected patients with NSCLC
Country: International

Aim: To evaluate the impact of adjuvant cisplatin+vinorelbine in completely resected patients with NSCLC and to identify patients who are likely to benefit from this regimen in the Lung Adjuvant Cisplatin Evaluation (LACE) database

Inclusion criteria
Randomised trials with N > 300 that were performed after the NSCLC meta-analysis published in 1995 (Non-Small Cell Lung Cancer Collaborative Group, 1995) comparing cisplatin-based adjuvant chemotherapy versus observation in patients with completely resected NSCLC surgery alone.

Exclusion criteria
Trials using concomitant radiochemotherapy or preoperative chemotherapy, included incompletely resected patients or were included in the 1995 NSCLC meta-analysis.

Population
The 5 studies were divided into two subgroups according to the type of chemotherapy administered:
Cisplatin + vinorelbine (compared to observation): N = 1888 from 4 studies.
Other (i.e., not cisplation+vinorelbine) chemotherapy (compared to observation): N = 2696 from 3 studies.
Median follow-up = 5.2 years in both group

Interventions
Adjuvant chemotherapy: Surgery + chemotherapy (Cisplatin + vinorelbine v other [i.e., not cisplatin + vinorelbine])
Control: Surgery alone

Outcomes

Overall survival, time-to-recurrence (disease/progression-free survival)

Results

Survival (all patients): There was an interaction between the effect of chemotherapy on survival and the type of chemotherapy used (p = .04): This interaction reflected better survival in the cisplatin + vinorelbine group (Hazard ratio (HR) = **.8 (95% CI .7-.91; p < .001; I^2 = 0%, i.e., no heterogeneity)** favouring adjuvant chemotherapy over observation) than in the other adjuvant chemotherapy group (HR = .95 (95% CI .86-1.05, p = .33)). The absolute benefit in the cisplatin + vinorelbine group over observation = 6.8% at 3 years and 8.9% at 5 years.

Cisplatin-vinorelbine patients:

- **Multivariate analyses showed that chemotherapy (HR = .76) and squamous histology (HR = .69) were associated with longer survival and that pneumonectomy (HR = 1.33), age (HR = 1.26 for 51-60 years; HR = 1.4 for 61-69 years and HR = 1.9 for ≥ 70 years) and stage (HR = 1.72 for stage II and HR = = 2.61 for stage III) were associated with significantly shorter survival.** Gender was not significantly associated with survival, and chemotherapy did not interact with gender, performance status, age, histology, type of surgery and planned radiotherapy.
- Chemotherapy treatment interacted with stage (I^2 = 31%, i.e., some heterogeneity): HR = 1.01 (95% CI .78-1.3, ns) for stage I, HR = .74 (95% CI .6-.91; significant) favouring chemotherapy for stage II and HR = .66 (95% CI .53-.83) favouring chemotherapy for stage III.

Other patients:

- Chemotherapy did not interact with stage.

Disease-free survival (all patients): There was an interaction between the effect of chemotherapy on disease-free survival and the type of chemotherapy used (p = .02): This interaction reflected better disease-free survival in the cisplatin + vinorelbine group (HR = **.75 (95% CI .67-.85; p < .001; I^2 = 0%, i.e., no heterogeneity)** favouring adjuvant chemotherapy over observation) than in the other adjuvant chemotherapy group (HR = .9 (95% CI .82-.99, p = .04; I^2 not reported). The absolute benefit in the cisplatin + vinorelbine group over observation = 10% at 3 years and 9.2% at 5 years. The absolute benefit in the other group over observation = 3.8% at 5 years.

Cisplatin-vinorelbine patients:

- Chemotherapy treatment interacted with stage (I^2 = 34%, i.e., some heterogeneity): HR = .95 (95% CI .76-1.19, ns) for stage I, HR = .69 (95% CI .57-.83; significant) favouring chemotherapy for stage II and HR = .62 (95% CI .5-.76) favouring chemotherapy for stage III.

Other patients:

- Chemotherapy did not interact with stage.

Cancer- and noncancer-related deaths:

-Drug-related deaths = 1.4% in the cisplatin + vinorelbine group and .4% in the other group
- Interaction with time in both chemotherapy groups for noncancer deaths
- Cisplatin + vinorelbine:
    1. Whole follow-up period: The Chemotherapy and observation patient groups did not differ in rates of noncancer-related deaths (HR = 1.31, 95% CI .91-1.88, p = .15), **but chemotherapy was associated with significantly less cancer-related deaths (HR = .74, 95% CI .65-.85, p < .001).**
    2. Months 0-6 of the follow up period: **Significantly more nonlung cancer deaths were observed in the chemotherapy group than in the observation group (HR = 2.92 (95% CI 1.54-5.51, p < .001**)
- Other:
    1. Whole follow-up period: **Chemotherapy was associated with significantly more noncancer-related deaths (HR = 1.4, 95% CI 1.08-1.82, p = .001).**
    2. Months 0-6 of the follow up period: **Significantly more nonlung cancer deaths were observed in the chemotherapy group than in the observation group (HR = 2.17 (95% CI 1.33-3.53, p = .002)**

General comments

The original search strategy that the selection of papers in this meta-analysis is based on cannot be evaluated. It is therefore unknown whether all relevant trials have been identified and whether the results are subject to publication bias. Although the analyses were performed according to the intention to treat principle, the I^2 value is not reported for some of the analyses making it difficult to fully evaluate between-study heterogeneity, and consequently the validity of the observed results. These results must therefore be interpreted with caution. The evidence provided by this meta-analysis can therefore only be considered of moderate quality.

References of Included Studies (for systematic review):

-Non-Small Cell Lung Cancer Collkaborative Group (1995). Chemotherapy in non-small cell lung cancer: A meta-analysis

using updated data on individual patients from 52 randomized clinical trials. BMJ, 311, 899-909.
-Pignon, J.P, Tribodet, H., Scagliotti, G.V., Douillard, J.Y., Shepherd, F.A>, Stephens, R.J., Dunant, A., Torri, V., Rosell, R., Seymour, L., Spiro, S.G., Rolland, E., Fossati, R., Aubert, D. Et al. (2008). Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE Collaborative Group. Journal of Clinical Oncology, 26, 3552-3559.
- Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II or IIIa non-small cell lung cancer. *J Natl Cancer Inst* 2003; **95:** 1453–61.
- Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006; **7:** 719–27.
- The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. *N Engl J Med* 2004; **350:** 351–60.
- Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004; **26:** 173–82.
- Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs observation in resected non-small cell lung cancer. *N Engl J Med* 2005; **352:** 2589–97.

Citation: Felip,E.; Rosell,R.; Maestre,J.A.; Rodriguez-Paniagua,J.M.; Moran,T.; Astudillo,J.; Alonso,G.; Borro,J.M.; Gonzalez-Larriba,J.L.; Torres,A.; Camps,C.; Guijarro,R.; Isla,D.; Aguilo,R.; Alberola,V.; Padilla,J.; Sanchez-Palencia,A.; Sanchez,J.J.; Hermosilla,E.; Massuti,B. (2010). Preoperative Chemotherapy Plus Surgery Versus Surgery Plus Adjuvant Chemotherapy Versus Surgery Alone in Early-Stage Non-Small-Cell Lung Cancer. Journal of Clinical Oncology, 28, 3138-3145.

Design: Multi-centre RCT
Country: Europe

Aim: To assess whether disease-free survival is prolonged by neoadjuvant chemotherapy + surgery or surgery +adjuvant chemotherapy compared to surgery alone in patients with resectable NSCLC.

Inclusion criteria
-clinical stage IA with tumour size > 2 cm, IB, II, or T3N1 resectable NSCLC
-age ≥ 18 years
-ECO G performance status 0-2
-no previous chemotherapy or radiotherapy
-adequate hematologic, hepatic, and renal function.
-fit for chemotherapy and for the proposed surgical resection.

Exclusion criteria
- previous cancer other than nonmelanoma skin cancer or carcinoma in situ of the cervix
-clinically significant cardiac dysfunction
-active infection
-neurologic or psychiatric disorders.

Population
Controls: N = 210; median age 64 (range 36-89) years; 184 males; ECOG PS 0/1/2/missing: N = 102/105/3/0; TNM stage T1N0 / T2N0 / T1N1 / T2N1 / T3N0 / T3N1 / T4N0: N = 20/134/1/25/26/4/0; Histology squamous/ adeno/ large cell/other: N = 105/71/21/13.
Neoadj: N = 199; median age 65 (range 35-80) years; 175 males; ECOG PS 0/1/2/missing: N = 88/108/1/2; TNM stage T1N0 / T2N0 / T1N1 / T2N1 / T3N0 / T3N1 / T4N0: N = 16/132/4/24/18/4/1; Histology squamous/ adeno/ large cell/other: N = 107/57/21/1.
Adj: N = 210; median age 64 (range 33-81) years; 181 males; ECOG PS 0/1/2/missing: N = 95/111/3/1; TNM stage T1N0 / T2N0 / T1N1 / T2N1 / T3N0 / T3N1 / T4N0: N = 30/133/3/25/18/1/0; Histology squamous/ adeno/ large cell/other: N = 103/69/24/14.

Interventions
Surgery alone (control): Surgery consisted of lobectomy, bilobectomy, or pneumonectomy (according to the baseline CT scan of the chest and took place as soon as possible after randomisation.
Neoadjuvant chemotherapy followed by surgery (neoadj): Chemotherapy consisted of three 3-weekly cycles of 200 mg paclitaxel per square meter of body surface area, administered intravenously over 3 hours followed immediately by

carboplatin (AUC dose of 6.0 mg/mL/min, administered intravenously over a period of 30-60 minutes) and had to start as soon as possible after randomization. Surgery took place within 3-4 weeks after the completion of chemotherapy
Surgery followed by adjuvant chemotherapy (adj): Surgery as per control group followed within3-5 weeks by chemotherapy as per the neoadj group.
Postoperative thoracic radiotherapy was allowed in patients with pathologic N2 disease at surgery.

Outcomes
Disease-free survival, overall survival, adverse events

Results *Median follow up = 51 months*
Surgery and chemotherapy delivery and toxicity:
-Neoadj patients: 180 patients completed all three planned chemotherapy cycles, 9 patients had two cycles, and 4 patients received one cycle. Of the patients receiving chemotherapy, 9.3% had dose reductions, and 11.4% had one or more dose delays. Overall response rate was 53.3% (18 CRs, 88 PRs and 63 SDs, 11 PDs, 19 non-evaluable)
-Adj patients: 128 patients received the planned three chemotherapy cycles, 8 patients had two cycles, and 3 patients had 1 cycle. Of the patients receiving adjuvant chemotherapy, 10.8% had ≥ 1 dose reduction, and 15.8% had one or more dose delays. 71 patients did not start the planned chemotherapy.
-More neoadj patients started the planned chemotherapy treatment than adj patients (97% *v* 66.2%; p < .0001).
-Grade 3-4 toxicity: The incidence rates of neutropenia, thrombocytopenia, anemia, nausea & vomiting, febrile neutropenia, diarrhea, hyperglycemia, arthralgias, myalgias, fatigue, sensory neuropathy, and allergic reactions did not differ significantly between the neoadj and adj groups (all ps ≥ .09).
-1 adj and 1 neoadj patient died due to chemotherapy-related toxicity (bone marrow aplasia & hypovolemic shock, anaphylaxis to carboplatin).
-10 control patients with pathologic N2 disease received adjuvant chemotherapy.
-200 patients in the control group, 181 patients in the neoadj group, and 201 patients in the adj group underwent surgery.
-11 control patients, 9 neoadj patients, and 15 adj patients died postoperatively.
Disease-free survival: All patients:
-3- and 5-year disease-free survival rates = 41.9% and 34.1% in the control group, 48.4% and 38.3% in the neoadj group, and 44.9% and 36.6% in the adj group; the 5-year disease-free survival rates were 34.1%, 38.3%.
-HR for progression or death in the neoadj group relative to the control group = .92 (95% CI .81- 1.04; non-significant).
-HR for progression or death in the adj group relative to the control group = .96 (95% CI.75-1.22; non-significant).
These results did not vary with age, gender, ECOG performance status, pretreatment clinical stage or type of surgery
Survival: All patients:
109 control patients, 99 neoadj patients, and 102 adj patients died. 5-year survival rates = 44%, 46.6%, and 45.5% in the control, neoadj and adj groups, respectively. The groups did not differ statistically significantly in overall survival.
Survival: Stage II-T3N1 patients:
-5-year survival rates = 34.5% in the control group, 41.3% in the neoadj group, and 36.6% in the adj group.
-HR for death in the neoadj group relative to the control group = .88 (95% CI .69-1.12; non-significant)
-HR for death in the adj group relative to the control group = 1.01 (95% CI .62-1.65; non-significant).

General comments
The patients included in this trial were centrally randomised by fax with stratification for tumour size and age. No further details about the randomization technique employed are reported. Although no detail is reported about allocation concealment either, it is likely that central randomisation has gone some way in ensuring allocation concealment. The study appears to be adequately powered and the analyses were conducted according to the intention to treat principle. However, no blinding (e.g., of assessor of recurrence) appears to have been employed. The evidence provided by this RCT can therefore be considered of moderate quality.

References of Included Studies: N/A

Citation: Gilligan,D.; Nicolson,M.; Smith,I.; Groen,H.; Dalesio,O.; Goldstraw,P.; Hatton,M.; Hopwood,P.; Manegold,C.; Schramel,F.; Smit,H.; Van,Meerbeeck J.; Nankivell,M.; Parmar,M.; Pugh,C.; Stephens,R. (2007).
Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. Lancet, 369, 1929-37.

Design: RCT (& meta-analysis)
Country: International

Aim: To assess the efficacy of platinum-based neo-adjuvant chemotherapy + surgery compared to surgery alone in patients with any stage operable NSCLC

Inclusion criteria

Patients
-with previously untreated, histologically/cytologically proven NSCLC considered resectable
-with WHO performance status 0–2
-no evidence of distant metastases
-fit for chemotherapy and the proposed surgical resection
-with no other disease or previous malignancy likely to interfere with the protocol treatments or comparisons

Exclusion criteria

Population

Chemotherapy + surgery: N = 258 (median age 62 years; 186 males; WHO PS 0/1/2: N = 139/114/5; clinical stage at randomisation 1/2/3: 165/72/21; NP/CisGem regimen: N = 116/64)
Surgery alone: N = 261 (median age 63 years; 188 males; WHO PS 0/1/2: N = 144/113/4; clinical stage at randomisation 1/2/3: 154/91/16; NP/CisGem regimen: N = 100/66)

Interventions

Neo-adjuvant chemotherapy: 3 cycles of one of the following regimens:
MVP: Mitomycin 8 mg/m^2 (first two cycles only) + Vinblastine 6 mg/m^2 (max 10 mg) + Cisplatin 50 mg/m^2
MIC: Mitomycin 8 mg/m^2 (first two cycles only) + Ifosfamide 3 g/m^2 + Cisplatin 50 mg/m^2
NP: Day 1: Cisplatin 80 mg/m^2, Days 1 and 8: Vinorelbine 30 mg/m^2 (maximum 60 mg)
PacCarbo: Paclitaxel 175 mg/m^2, Carboplatin AUC5 ([EDTA GFR or measured creatinine clearance +25] x5) mg
GemCis: Day 1: Cisplatin 80 mg/m^2, Days 1 and 8: Gemcitabine 1250 mg/m^2
DocCarbo: Docetaxel 75 mg/m^2, Carboplatin AUC6

Post-operative radiotherapy was not generally recommended. However, on progression or patients found to be inoperable at surgery, treatment of the patient was left to the discretion of the treating physician.

Outcomes

Survival, toxicity

Results

Chemotherapy/symptom changes:
-194/258 received the full course of 3 cycles
-Response: 120/247 who received at least one cycle of chemotherapy had a response (9 patients had complete response, 111 had partial response). 69 patients had stable disease and 5 patients had progressive disease. 53 patients were not assessed after their last cycle of chemotherapy, but 10/53 patients progressed on during chemotherapy.
Surgery:
- Reduction in the frequency moderate to severe of symptoms/morbidity during chemotherapy: Cough (from 37 [20%] to 16 [7%]), breathlessness (from 31 [17%] to 20 [9%]) and haemoptysis (from 10 [5%] to 3 [1%]).
-Increase in chest pain: Surgery alone group (from 13 [6%] of 229 pre-surgery to 14 [14%] of 97 patients 3 months post-surgery), chemotherapy group (12 [5%] of 234 patients post-chemotherapy and pre-surgery rising to 15 of 143 (10%) 3 months post-surgery).
Quality of life:
At 6 months the chemotherapy group scored significantly lower on the role physical domain (problems with work or other daily activities as a result of physical health) compared to the surgery alone group (p=0.002) and compared to the scores by the chemotherapy group at baseline (p=0.044). No other significant differences were reported.
Time to progression:
The estimated median progression-free survival (PFS) and 2-year PFS = 25 months and 52% in the surgery alone group and 26 months and 53% for the chemotherapy group, respectively. PFS did not differ between the treatment groups (hazard ratio = .96, 95% CI .77-1.21; ns).
Survival:
244/519 patients had died at the time of analysis (N = 122 in both groups). The cause of death was considered to be lung cancer in 91 and 87 patients, treatment-related in 8 and 9 patients, 'other' in 7 and 14, and 'currently unknown' in 16 and 12 patients in the surgery alone and chemotherapy groups, respectively. One death was considered to be related to

chemotherapy.
Overall survival did not differ between the two treatment groups (hazard ratio = 1.02 (95% CI .8-1.31; ns).
Estimated median and 5-year survival rate = 55 months and 45% for the surgery alone group and 54 months and 44% for the chemotherapy group.

The authors added their results to the meta-analysis by Burdett et al. (2007):
Overall Survival:
Hazard ratio = .88 (95% CI .76-1.01; ns; no heterogeneity evident).
Please note that these data are also included in the meta-analysis by Song et al. (2010)

General comments
The patients included in this trial were randomised with stratification for participating centre, histology, WHO performance status, and clinical T and N stage. In addition, the clinician had to indicate the chemotherapy regimen that would be offered to a patient before randomisation and on a patient-by-patient basis in case their patient was allocated to the chemotherapy group. No additional detail was reported about the randomisation method or whether allocation concealment was employed although it would appear that randomisation was central and therefore would go some way in ensuring allocation concealment. The analyses were conducted according to the intention-to-treat principle and the meta-analysis showed no heterogeneity. The evidence provided by this RCT/meta-analysis can therefore be considered of moderate-high quality.

References of Included Studies:
Burdett, S, Stewart, L., & Rydzewska, L. (2007). Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. Cochrane Database of Systematic Reviews: Reviews 3.

Citation: Hamada,C.; Tanaka,F.; Ohta,M.; Fujimura,S.; Kodama,K.; Imaizumi,M.; Wada,H. (2005). Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer. Journal of Clinical Oncology, 23, 4999-5006

Design: Meta-analysis
Country: International

Aim: To assess the efficacy of adjuvant chemotherapy with tegafur-urasil (UFT) in patients with NSCLC

Inclusion criteria
RCTs of patients with completely resected NSCLC comparing surgery alone to surgery + adjuvant UFT assessing chemotherapy with at least 5 years post-operative follow up.

Exclusion criteria
Trials comparing surgery alone to surgery + adjuvant intravenous chemotherapy and UFT

Population
6 studies with 2082 previously untreated patients < 76 years old with pathological stage I-II patients and no multiple cancer.
NOTE: 1 trial restricted to patients with stage I adenocarcinoma contributed almost 50% of the patients.

Interventions
Adjuvant chemotherapy: Surgery + UFT
Control: Surgery alone.

Outcomes
Survival

Results
Survival (all patients; intention-to-treat analysis):
Hazard ratio = **.76 (95% CI .64-.9; p = .005**) favouring adjuvant UFT. That is, UFT chemotherapy is associated with an overall 24% reduction in the risk of death relative to surgery alone (no significant heterogeneity evident).
This pattern of results remained even when taking age, sex, histological subtype and pathological T- and N-stage into account (hazard ratio = **.75 (95% CI .63-.9; p = .002)** using multivariate analysis.

General comments

In this article, the details and full results of the literature search are not reported, potential publication bias was not addressed, and the quality of the included studies is not assessed. These limitations introduce the potential for various biases and this must be kept in mind when evaluating the results. However, a good level of patient detail is reported and no heterogeneity between the included studies was found in the analyses. The evidence provided by this meta-analysis can therefore be considered of moderate quality.

References of Included Studies (for systematic review):

-Endo, C., Saito, Y., Iwanami, H., Tsushima, T., Imai, T., Kawamura, M. et al. (2003). A randomized trial of postoperative UFT therapy in p stage I, II non-small cell lung cancer: North-east Japan Study Group for Lung Cancer Surgery. *Lung cancer (Amsterdam, Netherlands), 40,* 181-186.
-Imaizumi, M. (2003). A randomized trial of postoperative adjuvant chemotherapy for p-stage I non-small cell lung cancer (4th cooperative study). *Lung cancer, 41,S2 (abstr O180)*.
-Kato, H., Ichinose, Y., Ohta, M., Hata, E., Tsubota, N., Tada, H. et al. (2004). A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *The New England journal of medicine, 350,* 1713-1721.
-Nakagawa,M.; Tanaka,F.; Tsubota,N.; Ohta,M.; Takao,M.; Wada,H.; West Japan Study Group for Lung Cancer Surgery (2005). A randomized phase III trial of adjuvant chemotherapy with UFT for completely resected pathological stage I non-small-cell lung cancer: the West Japan Study Group for Lung Cancer Surgery (WJSG)--the 4th study. *Annals of Oncology, 16*, 75-80.
-Tada, H., Yasumitsu, T., Iuchi, K., et al. (2002). Randomized study of adjuvant chemotherapy for completely resected non-small cell lung cancer. Proc J Clin Oncol, 21, 313a (abstr 1250).
-Wada, H., Hitomi, S., Teramatsu, T., West Japan Study Group for Lung Cancer Surgery (1996). Adjuvant chemotherapy after complete resection in non-small-cell lung cancer. *Journal of Clinical Oncology, 14*, 1048-54.

Citation: Hanna, N., Neubauer, M., Yiannoutsos, C., McGarry, R., Arseneau, J., Ansari, R. et al. (2008). Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *Journal of clinical oncology, 26,* 5755-5760.

Design: RCT
Country: USA

Aim: To assess the efficacy of consolidation docetaxel (compared to observation) after concurrent chemoradiation in patients with inoperable stage III NSCLC.

Inclusion criteria
1) Baseline: Patients with
-cytologically/histologically confirmed stage IIIA or IIIB previously untreated, measurable/assessable, inoperable NSCLC
-unintended weight loss < 5% within the 3 months preceding study start
-ECOG performance status (PS) = 0 or 1 at baseline
-adequate bone marrow, renal and liver function
-preregistration forced expiratory volume (FEV) in 1s ≥ 1 L by spirometry within 42 days of study treatment
2) Consolidation therapy: Patients with
-completion of initial chemoradiation within 4-8 weeks of random assignment without local progression or distant metastases
-ECOG PS = 0-2 at random assignment
-adequate bone marrow and hepatic function
-absence of peripheral neuropathy before random assignment

Exclusion criteria
Patients with
-disease extending into the cervical region
-symptomatic peripheral neuropathy (≥ grade 1) at baseline
-malignant pleural or pericardial effusions
-superior sulcus tumours
-significant cardiac disease

Population
Doc: N = 73 (median age 62 years; 34.2% females; PS 0: 57.5%; stage IIIA: 42.5%; current smoker: 50%; FEV in 1 s > 2 L:

41.1%).
Obs: N = 74 (median age 62 years; 25.7% females; PS 0: 59.5%; stage IIIA: 39.2%; current smoker: 43.9%, FEV in 1 s > 2 L: 59.5%).
The groups did not differ statistically from each other or from the patients who were entered into the study but not randomly assigned (all ps ≥ .066).

Interventions
All patients: Cisplatin 50 mg/m^2 IV on days 1, 8, 29 and 36 + etoposide 50 mg/m^2 on days 1-5 and 29-33. Concurrent radiotherapy consisting of 59.4Gy/33 fractions of 1.8 Gy 5 days a week followed by random assignment to observation (Obs) or consolidation docetaxel (Doc):
Doc: Three 21-day cycles of docetaxel 75 mg/m^2 IV (on day 1?).

Outcomes
Survival, toxicity.

Results
Chemotherapy delivery and toxicity:
-80.8%, 8.2%, and 6.9% of the Doc patients completed 3, 2 and 1 of the docetaxel cycles. 4.1% of the Doc patients did not receive docetaxel. 32.4% Doc patients received granulocyte colony-stimulating factor support.
-Grade 3-4 haematologic toxicities in the Doc patients: Anaemia (1.3%), neutropenia (24.7%), febrile neutropenia (10.9%), thrombocytopenia (0%).
-Grade 3-5 non-haematologic toxicities in the Doc and Obs patients, respectively**: Infections (11% and 0%; p = .003); pneumonitis (9.6% and 1.4%; p < .001)**; treatment-related deaths (5.5% and 0%; p = .058)
-28.8% of Doc and 8.1% of Obs required hospitalization during the 9 weeks after random assignment
-5.5% of Doc and 1.4% of the Obs patients required blood transfusions (p = .21)
Survival:
July 2006: 30 deaths in the Doc group and 32 deaths in the Obs group (p = .91)
December 2007: 50 deaths in each group after a median follow up time of 41.6 months.
-Median overall survival = 21.2 months in the Doc patients and 23.2 months in the Obs patients (p = .88).
-The 3-year survival rates = 27.1% and 26.1% in the Doc and Obs patients, respectively.
-Progression-free survival did not differ between the groups, either

General comments
Although the patients in this trial were randomised with stratification for stage (IIIA v IIIB), performance status (0-1 v 2) and initial response (CR v not CR), it is unclear which randomisation method was employed and it appears that no allocation concealment was ensured. In addition, no level of blinding appears to have been employed including for the assessment of outcomes other than death. The trial was closed early due to a finding of futility by a data and safety monitoring board. The evidence provided by this RCT can therefore be considered to be of low-moderate quality.

References of Included Studies: NA

Citation: Hotta,K.; Matsuo,K.; Ueoka,H.; Kiura,K.; Tabata,M.; Tanimoto,M. (2004). Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials. Journal of Clinical Oncology, 22, 3860-3867.

Design: Meta-analysis
Country: International

Aim: To assess the efficacy of adjuvant chemotherapy in patients with NSCLC

Inclusion criteria
RCTs of patients with pathologically proven NSCLC who underwent curative resection comparing surgery alone to surgery + adjuvant chemotherapy.
Thoracic radiotherapy was allowed as one of the adjuvant treatments

Exclusion criteria
Trials comparing surgery alone to surgery + adjuvant chemotherapy + radiotherapy or to surgery + radiotherapy, and trials evaluating adjuvant immunotherapy, neoadjuvant chemotherapy and/or radiotherapy

Population

11 studies with 5716 patients

Interventions
Adjuvant chemotherapy: CDDP (8 studies/3907 patients) + vindesine (6/8 studies), single-agent UFT (5 studies /1809 patients).
Control: Surgery alone.

Outcomes
Overall survival, toxicity

Results
Overall survival (all patients):
Hazard ratio = **.872 (95% CI .805-.944; p = .001**) favouring adjuvant chemotherapy. That is, adjuvant chemotherapy is associated with an overall 12.8% reduction in the hazard (risk) of death relative to surgery alone (no significant heterogeneity evident).
Overall survival CDDP-containing regimens (3786 patients):
Hazard ratio = **.891 (95% CI .815-.975; p = .012**) favouring adjuvant chemotherapy. That is, adjuvant chemotherapy is associated with an overall 10.9% reduction in the hazard (risk) of death relative to surgery alone.
Overall survival single-agent UFT (1751 patients):
Hazard ratio = **.799 (95% CI .668-.957; p = .015**) favouring adjuvant chemotherapy. That is, adjuvant chemotherapy is associated with an overall 20.1% reduction in the hazard (risk) of death relative to surgery alone.
Toxicity (2594/2873 patients assigned to adjuvant chemotherapy):
Patients on CDDP-based chemotherapy:
-Grade 4: Neutropenia (14%), thrombocytopenia (2%),
-Grade 3+: Nephrotoxicity (2%), nausea and vomiting (10%), respectively, of
Patients on UFT-chemotherapy:
-Grade 3+: Nausea and vomiting (.7%), diarrhea (.2%), hepatic toxicity (.2%).
Treatment related deaths: 16 (0.6%) in 10 trials (2,559 assessable patients assigned to adjuvant chemotherapy).

General comments
Although the authors searched for both published and unpublished trials with this intention of ensuring that there was no publication bias, this strategy is limited by the exclusion of non-English language trials. The quality of all the included trials was basically assessed, although not for whether allocation concealment was employed or not. These limitations introduce the potential for various biases and this must be kept in mind when evaluating the results. However, no heterogeneity between the included studies was found in the analyses. The evidence provided by this meta-analysis can therefore be considered of moderate quality.

References of Included Studies (for systematic review):
-Arriagada, R., Bergman, B., Dunant, A., Le, C. T., Pignon, J. P., Vansteenkiste, J. et al. (2004). Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *The New England journal of medicine, 350,* 351-360.
-Endo, C., Saito, Y., Iwanami, H., Tsushima, T., Imai, T., Kawamura, M. et al. (2003). A randomized trial of postoperative UFT therapy in p stage I, II non-small cell lung cancer: North-east Japan Study Group for Lung Cancer Surgery. *Lung cancer (Amsterdam, Netherlands), 40,* 181-186.
-Imaizumi, M. (2003). A randomized trial of postoperative adjuvant chemotherapy for p-stage I non-small cell lung cancer. *Proc World Conference on Lung cancer, 41*, 54 (abstr O-180).
-Kato, H., Ichinose, Y., Ohta, M., Hata, E., Tsubota, N., Tada, H. et al. (2004). A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *The New England journal of medicine, 350,* 1713-1721.
-Minoe, T.C., Ambrogi, V., Corsaro, V., & Roselli M. (2001). Postoperative adjuvant therapy for stage IB non-small cell lung cancer. *European Journal of Cardiothoracic Surgery, 20*, 378-84.
-Scagliotti, G. V., Fossati, R., Torri, V., Crinò, L., Giaccone, G., Silvano, G. et al. (2003). Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer. *Journal of the National Cancer Institute., 95,* 1453-1461.
-Tada, H., Yasumitsu, T., Iuchi, K., et al. (2002). Randomized study of adjuvant chemotherapy for completely resected non-small cell lung cancer: Lack of prognostic significance in DNA ploidy pattern at adjuvant setting. *Proc Am Soc Clin Oncol, 21*, 313 (abstr 1250).
-Tada, H., Tsuchiya, R., Ichinose, Y., Koike, T., Nishizawa, N., Nagai, K. et al. (2004). A randomized trial comparing adjuvant chemotherapy versus surgery alone for completely resected pN2 non-small cell lung cancer (JCOG9304). *Lung cancer (Amsterdam, Netherlands), 43,* 167-173.

-Tanaka, F., & Wada, H. (2001). Postoperative oral administration of UFT for completely resected pathological stage I non-small cell lung cancer: The West Japan study group for lung cancer surgery (WJSG), the 4th study. *European Journal of Cancer, 37,* 29 (abstr 96).
-Waller, D., Fairlamb, D.J., Gower, N., et al. (2003). The Big Lung Trial (BLT): Determining the value of cisplatin-based chemotherapy for all patients with non-small cell lung cancer (NSCLC) – Preliminary results in the surgical setting. *Proc Am Soc Clin Oncol, 22*, 632 (abstr 2543).
-Xu, G., Rong, T., & Lin, P. (2000). Adjuvant chemotherapy following radical surgery for non-small-cell lung cancer: A randomized study on 70 patients. Chinese Medical Journal (Engl), 113, 617-20

Citation: Ichinose, Y., Genka, K., Koike, T., Kato, H., Watanabe, Y., Mori, T. et al. (2003). Randomized double-blind placebo-controlled trial of bestatin in patients with resected stage I squamous-cell lung carcinoma. *Journal of the National Cancer Institute., 95,* 605-610.

Design: RCT
Country: Japan

Aim: To assess the efficacy of adjuvant treatment with bestastin compared to placebo in patients with completely resected stage 1 squamous-cell lung cancer.

Inclusion criteria
Patients with
-completely resected pathologically confirmed stage I squamous-cell carcinoma
-aged 40-75 years
-ECOG performance status 0–2
-no anti-cnacer treatment before resection
-no previous or synchronous cancer
-adequate organ function after surgery

Exclusion criteria

Population
Bestatin (B): N = 202 (mean age 65 years; 181 males; ECOG PS 0/1/2: N = 117/81/4; tumour status Tis/1/2/3: N = 0/99/103/0; type of resection: lobectomy/pneumonectomy/segmentectomy: N = 197/5/0). 1 patient did not receive any active drug.
Placebo (P): N = 198 (mean age 66 years; 180 males; ECOG PS 0/1/2: N = 125/65/8; tumour status Tis/1/2/3: N = 2/95/100/1; type of resection: lobectomy/pneumonectomy/segmentectomy: N = 189/8/1). 3 patients did not receive any placebo.

The groups did not differ in age, gender, performance status, tumour status, tumour location, type of resection, whether proportion of patients receiving a blood transfusion.

Interventions
B: Daily capsule of 30 mg bestatin by oral administration after breakfast.
P: Daily capsule of vehicle without bestatin by oral administration after breakfast.

Treatment commenced within 1 week of randomization which was performed within 28 days of resection.

Outcomes
Survival, toxicity.

Results
Treatment delivery:
-12 B and 11 P patients discontinued treatment due to adverse reactions after a mean of 162 (range 7-644) days and 114 (range 11-504) days, respectively.
-97.6% and 96.3% of the projected B and P doses were administered.
Toxicity (data from 201/202 B patients and 195/198 P patients):
-Grade 1/2, 3 and 4 leucopenia: <1, 0 and 0% in B patients and 3, <1and 0% in the P patients, respectively (ns) -Grade 1/2, 3 and 4 thrombocytopenia: 2, 0 and 0% in B patients and <1, 0 and 1% in the P patients, respectively (ns)
-Grade 1/2, and 3 anorexia: 12 and 3% in B patients and 5 and 2% in the P patients, respectively (p = .013)

-Grade 1/2 and 3 nausea/vomiting: 5 and 2% in B patients and 3 and 2% in the P patients, respectively (ns)
-Grade 1/2 and 3 skin reaction: 4 and <1% in B patients and 9 and 0% in the P patients, respectively (ns)
-Grade 1/2, 3 and 4 serum glutamic-oxaloacetic transaminase: 5, <1 and 0% in B patients and 4, <1 and 0% in the P patients, respectively (ns)

Survival:

5-year survival rates = 81% and 74%, respectively in the B and P-groups. This is equal to a 5-year survival difference of 7% (95% CI -1.4-15%, ns). Overall survival did however differ between the groups ($p < .05$).

Cancer-free survival:

29% B- and 37% P-patients experienced recurrence or a secondary primary cancer as the first treatment-failure after surgery ($p = .066$).

5-year cancer-free survival rates = 71% and 62%, respectively in the B- and P-patients, which is equal to a difference of 9% (95% CI -.7%-17.8%, ns). **According to a Kaplan-Meier or Wilcoxon analysis, the 5-year cancer-free survival rates were statistically significantly different (ps = .017 and .022, respectively).**

The survival rates after diagnosis of either recurrence or second primary cancer did not differ significantly between the groups.

General comments

The patients included in this trial were centrally randomised with no stratification in blocks of six by a centralised masked-draw system combining coded numbers with drug allocation. Central randomisation is likely to have gone some way in ensuring adequate allocation concealment. Full blinding was used in this study including during analysis. The analyses were conducted on an intention-to-treat basis, but the results of cancer-free survival must be interpreted with caution because of the finding that the 5-year cancer-free survival rates differed significantly according to one type of analysis and not according to another. The evidence provided by this RCT can be considered of high quality.

References of Included Studies: NA

Citation: Kelly, K., Chansky, K., Gaspar, L. E., Albain, K. S., Jett, J., Ung, Y. C. et al. (2008). Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *Journal of clinical oncology, 26,* 2450-2456.

Design: RCT
Country: USA and Canada

Aim: To assess the efficacy of maintenance gefitinib (compared to placebo) after concurrent chemoradiation and consolidation docetaxel in patients with inoperable stage III NSCLC.

Inclusion criteria

Patients with
-pathologically confirmed stage IIIA or IIIB inoperable previously untreated NSCLC
-ECOG performance status (PS) = 0 or 1
-adequate organ function
-forced expiratory volume (FEV) in 1s < 2 L if min FEV = 800 mL in contralateral lung

Exclusion criteria

Patients with
-pleural or pericardial effusions
-multiple tumours within the lung

Population

Gef: N = 118 (median age 62 years; 79 males; race white/black: N = 114/4; PS at entry 0/1/unknown: N = 60/53/5; stage IIIA/IIIB at entry: N = 53/65; FEV at entry in 1 s ≥ 2 L/< 2 L/not reported: N = 91/26/1; best overall response to chemoradiation and consolidation CR/PR/SD: N = 6/75/37; histology adenocarcinoma/squamous cell carcinoma/other NSCLC/unknown: N = 35/36/46/1).

Obs: N = 125 (median age 61 years; 74 males; race white/black/Asian/other: N = 107/14/2/ 2; PS at entry 0/1/unknown: N = 70/50/5; stage IIIA/IIIB at entry: N = 64/61; FEV at entry in 1 s ≥ 2 L/< 2 L/not reported: N = 79/44/2; best overall response to chemoradiation and consolidation CR/PR/SD: N = 8/81/36; histology adenocarcinoma/squamous cell carcinoma/other NSCLC/unknown: N = 41/36/46/2).

The groups did not differ statistically from each other on the above characteristics apart from **race with a significantly higher proportion of non-whites assigned to the gefitinib group (p = .003).**

Interventions
All patients: Cisplatin 50 mg/m^2 IV on days 1, 8, 29 and 36 + etoposide 50 mg/m^2 on days 1-5, 29-33. Concurrent radiotherapy (RT) starting within 24 hours of chemotherapy consisting of 61 Gy delivered in fractions of 1.8-2 Gy per day. 4-8 weeks after RT, patients without progressive disease received three 21-day cycles of docetaxel 75 mg/m^2 on day 1. 3-6 weeks after last dose of docetaxel, patients were randomised to daily oral placebo (Pla) or gefitinib (Gef; 500 mg/day, initially, later changed to 250 mg/day) for 5 years.

Outcomes
Survival, toxicity.

Results
Gefitinib delivery and toxicity:
-52% Gef and 44% Pla patients stopped treatment with 6 months (p = .23) due primarily to disease progression.
-Grade 3-4 toxicities in ≥ 5% of the Gef patients: Pneumonitis (N = 3), rash (N = 8), diarrhea (N = 7), vomiting (N = 3). No treatment-related events occurred during gefitinib treatment.
Survival:
Oct 2006 after a median follow up time of 27 months.
-**Median overall survival = 23 months in the Gef patients and 35 months in the Pla patients (p = .013; HR = .633, 95% CI .44-.91).**
-The 1- and 2-year survival rates = 73% and 46% in the Gef patients and 81% and 59% in the Pla patients, respectively.
-Median progression-free survival = 8.3 months in the Gef patients and 11.7 months in the Pla patients (p = .17; HR = .8, 95% CI .58-1.1).
-Progression-free survival and overall survival did not differ between the Gef patients receiving 250 mg/day and 500 mg a day (both ps = .13).
Lung cancer was the primary reason for death in both groups (ns).

General comments
Although the patients in this trial were randomised and a placebo control was employed, it is unclear which randomisation method was employed and it appears that there was no allocation concealment or blinding on any level (e.g., for the assessment of outcomes other than death). The trial was closed early due to support for the alternative hypothesis. The evidence provided by this RCT can therefore be considered to be of low-moderate quality.

References of Included Studies: NA

Citation: Lu,C.; Lee,J.J.; Komaki,R.; Herbst,R.S.; Feng,L.; Evans,W.K.; Choy,H.; Desjardins,P.; Esparaz,B.T.; Truong,M.T.; Saxman,S.; Kelaghan,J.; Bleyer,A.; Fisch,M.J. (2010). Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. Journal of the National Cancer Institute, 102, 859-865.

Design: Multi-centre RCT
Country: USA

Aim: To assess the effect of adding AE-941 (a standardized aqueous shark cartilage extract with antiangiogenic properties) to chemoradiotherapy on overall survival of patients with unresectable stage III non–small cell lung cancer (NSCLC).

Inclusion criteria
Patients with
-histologically confirmed previously untreated, unresectable stage IIIA or IIIB NSCLC
-age ≥ 18 years
-ECOG performance status (PS) 0-1
-bidimensional or unidimensional measurable disease ≥10 mm,
-serum alanine aminotransferase and/or aspartate aminotransferase levels < 1.5 times the upper limit of normal,
-serum total bilirubin within normal limits,
-adequate renal function,
-adequate hematologic function

Exclusion criteria
Patients with
-pleural effusions (unless cytologically negative for malignant cells),

- > 10% weight loss within the past 3 months,
-use of cartilage-derived products within 30 days
-peripheral neuropathy > grade 1
-pregnancy/breast-feeding
-history of another malignant disease (except in situ carcinoma of the cervix or nonmelanoma skin cancer), unless curatively treated and without evidence of recurrent disease for > 3 years.

Population

Group AE-941 (AE-941): N = 188; median age 62.7 years (range 37.6-83.4); 111 males; ECOG PS 0/1/: N = 88/100; stage IIIA/IIIB: N = 81/107; chemotherapy regimens received Carboplatin + paclitaxel/cisplatin + vinorelbine: N = 109/79; Race white / black /other: N = 172/8/8; histology adeno/squamous/large cell/other or NOS: N = 76/63/13/36
Group placebo (PLA): N = 191; median age 62.9 years (range 36.9-84.4); 117 males; ECOG PS 0/1/: N = 90/101; stage IIIA/IIIB: N = 87/104; chemotherapy regimens received Carboplatin + paclitaxel/cisplatin + vinorelbine: N = 110/81; Race white / black /other: N = 175/9/7; histology adeno/squamous/large cell/other or NOS: N = 65/64/7/55.
The groups did not differ significantly on any of the above variables (all ps ≥ .09).

Interventions

All patients: Chemoradiotherapy treatment:
-Either two 3-weekly cycles of carboplatin (area under the concentration–time curve = 6) and paclitaxel (200 mg/m^2) followed by thoracic radiotherapy consisting of 60 Gy in 30 fractions initiated on day 50 with concurrent weekly carboplatin (area under the concentration–time curve 2) and paclitaxel (45 mg/m^2) for six doses.
-Or two 3-weekly cycles of cisplatin (75 mg/m^2, day 1) and vinorelbine (30 mg/m^2, days 1 and 8) followed by thoracic radiotherapy consisting of 60 Gy in 30 fractions initiated on day 50 with concurrent cisplatin (75 mg/m^2, day 1) and vinorelbine (15 mg/m^2, days 1 and 8) every 21 days for two cycles.

Group AE-941: 120 mL of oral AE-941 twice a day
Group placebo (PLA): 120 mL of oral placebo.
AE-941 or placebo were initiated at the start of chemoradiotherapy and continued until disease progression or the development of unacceptable toxic effects.

Outcomes

Survival, time to progression, progression-free survival, tumour response rate and toxicity.

Results *Trial closed early: 384/756 patients were recruited*

Median survival period = 14.4 months (95% CI 12.6-17.9 months) in the AE-941 group and = 15.6 months (95% CI 13.8-18.1 months) in the PLA group (non-significant). 1-, 3-, and 5-survival rates = 59%, 25%, and 14%, respectively, in the AE-941 patients and = 61%, 21%, and 14%, respectively, in the PLA patients.
The median time to progression = 11.3 months (95% CI 9-16.8 months) in the AE-941 patients and = 10.7 months (95% CI9.5-21.6 months) in the PLA patients (non-significant). "Similar results were obtained for the analyses with progression-free survival (data not shown)." Page 862).
Multivariate analysis of treatment group, stage of lung cancer, sex, and chemotherapy regimen revealed no significant predictors of overall survival or time to progression (all ps ≥ .07).
Response rate = 39% in the AE-941 patients and = 48% in the PLA patients (p = .12).
Toxicity (grade 3-5): The patients groups did not differ in the extent to which they experienced dyspnea, neutropenia, esophagitis, fatigue, pneumonitis, febril;e neutropenia, thrombocytopenia and anemia (all ps ≥ .38).
5% and 6% of the grade 3-5 adverse events were judged to be possibly or probably attributable to AE-941 and placebo, respectively (p = .26).
Total grade 3-5 adverse events = 66% in the AE-941 group and 77% in the PLA group (p = .018).
Deaths during the study period = 20 in the AE-941 group and 29 in the placebo groups. None of these deaths were attributed to either AE-941 or placebo.

General comments

The patients in this study were centrally randomised using a permuted block randomisation procedure with stratification for stage, chemotherapy regimen and gender. Although it is unclear whether there was allocation concealment, it is likely that central randomisation have gone some way in ensuring this. Furthermore, the trial was double-blind with placebo control, but makes no mention of treatment delivery/compliance and whether the analyses were conducted on an intention-to-treat basis. Due to early closure it would also appear that the study is underpowered. The evidence provided by this RCT can therefore be considered of low quality.

References of Included Studies: NA

Citation: Mattson, K. V., Abratt, R. P., ten, V. G., & Krofta, K. (2003). Docetaxel as neoadjuvant therapy for radically treatable stage III non-small-cell lung cancer: a multinational randomised phase III study. *Annals of Oncology, 14,* 116-122.

Design: RCT
Country: International

Aim: To assess the efficacy of neoadjuvant chemotherapy + surgery/curative intention radiotherapy (RT) (compared to surgery/curative intention RT alone) in patients with stage IIIA or locally treatable IIIB NSCLC.

Inclusion criteria
Patients with
-histologically/cytologically confirmed previously untreated NSCLC
-stage IIIA-N2 (T0-3) or T3 (N0-1) based on CT scan or locally treatable stage IIIB (T4, N3; "defined as disease suitable for curative-intention radiation therapy, of tumour stage T4 excluding malignant pleural effusion, or of nodal N3, and with the bulk of the tumour mass within 10 X 10 cm field with reasonable margins and not compromising vital structures." Page 117)
-age ≥ 18 years
-WHO performance status (PS) ≥ 2
-total white blood cell count ≥ 4.0 X 10^9/l
-absolute neutrophils (including bands) ≥ 1.5 X 10^9/l,
-platelets ≥ 100 X 10^9/l
-adequate hepatic and renal function

Exclusion criteria
Patients
-pregnant/lactating or women of child-bearing potential not using adequate contraceptive method
-aspartate aminotransferase > 3 X upper normal limit, alanine aminotransferase > 3 X upper normal limit or alkaline phosphatase > 6 X upper normal limit
-symptomatic peripheral neuropathy,
-previous/current malignancies
-uncontrolled infection
-other serious medical conditions

Population
Neo-adjuvant chemotherapy (NA-Ch): N = 134 (median age 61 years; 103 males; WHO PS 0-1/2/not defined: N = 115/18/1; tumour stage IIIA-T3/IIIA-N2/IIIB/not defined: N = 30/57/46/1; local treatment received Surgery/curative-intention RT/explorative surgery/explorative surgery + RT/none: N = 19/78/3/0/35). 89/134 completed the whole treatment protocol (i.e., NA-Ch + surgery/RT)
Surgery/RT alone (S/RT): N = 140 (median age 62 years; 117 males; WHO PS 0-1/2/not defined: N = 125/15/0; tumour stage IIIA-T3/IIIA-N2/IIIB/not defined: N = 32/64/44/0; local treatment received Surgery/curative-intention RT/explorative surgery/explorative surgery + RT/none: N = 25/102/1/3/9).

Interventions
NA-Ch: Chemotherapy treatment consisted of a maximum of three 3-weekly cycles of 100 mg/m^2 docetaxel administered as 1-hour IV infusion.
Surgery/RT was scheduled to commence within 6 weeks of day 1 of the third cycle, and managing clinician decided at baseline whether a given patient should be offered surgery or curative-intent RT based on extent of tumour dissemination and fitness for surgery.

Outcomes
Survival, toxicity.

Results
Chemotherapy delivery & toxicity:
-103/134 patients received all 3 planned cycles of chemotherapy
-N = 9 discontinued treatment due to an adverse event and 4/9 did not receive local treatment
-Events of grade 3-4 in N = 127 NA-Ch patients: Anaemia (3), leucopenia (56), thrombocytopenia (2), infection (10), neutropenia (96)

-Treatment-related deaths: N = 2

Non-haematological adverse events in 127/134 NA-Ch and 131/140 S/RT patients:

-Grade 3/4 events: Asthenia (NA-Ch: N = 9; S/RT: N = 3); cardiac dysrhythmias (NA-Ch: N = 0; S/RT: N = 4); diarrhoea (NA-Ch: N = 4; S/RT: N = 0); fever (NA-Ch: N = 1; S/RT: N = 0); (clinical) haemorrhage (NA-Ch: N = 3; S/RT: N = 2); neurocortical (NA-Ch: N = 4; S/RT: N = 0); neuromotor (NA-Ch: N = 5; S/RT: N = 2); oesophagitis (NA-Ch: N = 3; S/RT: N = 1); nausea (NA-Ch: N = 1; S/RT: N = 1); pain(NA-Ch: N = 8; S/RT: N = 4); pneumonia (NA-Ch: N = 3; S/RT: N = 1); pulmonary (NA-Ch: N = 13; S/RT: N = 9); skin (NA-Ch: N = 5; S/RT: N = 0); stomatitis (NA-Ch: N = 2; S/RT: N = 1); taste loss (NA-Ch: N = 0; S/RT: N = 0).

Survival and response:

-The 1-year survival rates = 59.1 (95% CI 50.4-67.7)% in the A-Ch group and 50.5 (95% CI 41.9-59.1)% in the S/RT group.
-The median survival time = 14.8 (95% CI 12.2-16.7) months in the NA-Ch group and 12.6 (95% CI 9.7-16) months in the S/RT group (ns). Median survival did not differ between the groups either when the patients were split by stage.
-Median time to progression = 9 (95% CI 7-11.9) months in the NA-Ch group and 7.6 (95% CI 6.4-9.7) months in the S/RT group (ns).
- Response rates = 28 (95% CI 19-38)% in the A-Ch group..

General comments

Although the patients in this trial were randomised, it is unclear which method of randomisation was used and whether allocation concealment was employed. The analyses were performed according to the intention-to-treat principle for effectiveness although only patients who received at least 2 cycles of docetaxel were eligible for response evaluation. The analyses of safety were performed according to treatment received. In addition, progression appears to have been assessed without blinding. The evidence provided by this RCT can therefore be considered of low-moderate quality.

References of Included Studies: NA

Citation: O'Rourke, N.; Roqué I Figuls, M.; Farré Bernadó, N.; Macbeth, F. (2010). Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database of Systematic Reviews: Reviews 6.

Design: Cochrane systematic review
Country: International

Aim: To assess the effectiveness of concurrent (C) chemoradiotherapy (ChRT) compared to radiotherapy (RT) alone in patients with stage I-III NSCLC; 2) To assess the effectiveness of concurrent C-ChRT compared to sequential (S) ChRT in patients with stage I-III NSCLC

Inclusion criteria

Published and unpublished randomised trials comparing C-ChRT to 1) RT alone or to 2) S-ChRT (including trials where additional chemotherapy had been given before/after/both before and after RT provided this was the same for both treatment groups) in patients with stage I-III NSCLC.

Exclusion criteria

Population

1) 19 trials with 2728 patients
2) 6 trials with 1024 patients

Interventions

1) Chemotherapy: 16/19 studies used platinum-based chemotherapy w/ etoposide (3/16); 3/19 used concurrent docetaxel or paclitaxel; 1/19 used hydroxyurea and 1/19 used hydroxycomptothecin. Administration of chemotherapy: Each RT treatment day (7/19; by continuous infusion in 1/7); once-weekly (6/19); and two- to four-weekly (8/19).
1) RT total dose = 60 Gy/30 fractions over 6 weeks (7/19 studies). 4/19 studies used accelerated or hyperfractionated regimes. 4/19 studies used a split course.
2) Chemotherapy: Cisplatin (6/6) + vinorelbine (4/6) + etoposide (C-ChRT group in 1/4) or + vinblastine (1/6)
2) RT total dose = 60-70.2 Gy

Outcomes See **Results** section

Results

1) C-ChRT versus RT alone

Overall Survival (9 trials): Hazard ratio (HR) = **.71 (95% CI .64.-.8; p < .00001; I^2 = 0%, i.e., no heterogeneity**) favouring C-

ChRT. That is, C-ChRT is associated with an overall 29% reduction in the risk of death relative to RT alone.
2-year survival:
-All 19 trials: **Risk ratio = .91 (95% CI .86-.97; p < .05; I^2 = 38%, i.e., some heterogeneity) favouring C-ChRT. Absolute survival benefit for C-ChRT = 8% (95% CI -12%- -3%; p = .00053; I^2 = 39%, i.e., some heterogeneity)**
-Platinum-containing regimens (16 trials): Risk ratio = .92 (95% CI .86-.98; p < .05; I^2 = 41%, i.e., heterogeneity) favouring C-ChRT.
-Taxane-containing regimens (2 trials): **Risk ratio = .82 (95% CI .71-.94; p < .05; I^2 = 0%, i.e., no heterogeneity) favouring C-ChRT.**
-Other(i.e., not platinum or taxane)-containing regimens (2 trials): Risk ratio = .88 (95% CI .56-1.36;ns; I^2 = 70%, i.e., heterogeneity).
A test for differences between the platinum-, taxene- and other-containing subgroups was not significant.
-Daily chemotherapy (7 trials): Risk ratio = .94 (95% CI .84-1.05; ns; I^2 = 55%, i.e., heterogeneity).
-Weekly chemotherapy (7 trials): **Risk ratio = .9 (95% CI .84-.96; p < .05; I^2 = 0%, i.e., no heterogeneity) favouring C-ChRT.**
-Two- to four-weekly chemotherapy (8 trials): Risk ratio = .9 (95% CI .81-.99; p < .05; I^2 = 41%, i.e., heterogeneity) favouring C-ChRT.
A test for differences between the daily, weekly and 2-4 weekly chermotherapy administration subgroups was not significant.
-2 trials varying the frequency of chemotherapy administration: Risk ratio = .91 (95% CI .8-1.03; ns; I^2 = 0%, i.e., no heteregeneity).
-Cisplatin > 150 mg/m^2 or carboplatin ≥ 700 mg/m^2 (9 trials): Risk ratio = .91 (95% CI .84-1; ns; I^2 = 40%, i.e., heteregeneity).
-Cisplatin < 150 mg/m^2 or carboplatin < 700 mg/m^2 (7 trials): Risk ratio = .93 (95% CI .84-1.03; ns; I^2 = 48%, i.e., heteregeneity).
A test for differences between the low and high dose platinum subgroups was not significant.
-Once-daily RT (15 trials): Risk ratio = .91 (95% CI .85-.97; p < .05; I^2 = 41%, i.e., heterogeneity).
-Twice-daily RT (5 trials): Risk ratio = .92 (95% CI .79-1.08; ns; I^2 = 40%, i.e., heterogeneity).
A test for differences between the once and twice daily RT subgroups was not significant.
-RT dose of 50-60 Gy (13 trials): Risk ratio = .93 (95% CI .86-1.01; ns; I^2 = 44%, i.e., heterogeneity).
-RT dose of 60-69.9 Gy (7 trials): Risk ratio = .88 (95% CI .81-.95; p < .05; I^2 = 21%, i.e., limited heterogeneity) favouring C-ChRT.
A test for differences between the low and high dose RT subgroups was not significant (I^2 = 46.7%).
-Follow up ≥ 22 months (7 trials): Risk ratio = .9 (95% CI .83-.97; p < .05; I^2 = 39%, i.e., some heterogeneity).
-Follow up < 22 months (4 trials): Risk ratio = .99 (95% CI .85-1.15; ns; I^2 = 24%,i.e., limited heterogeneity).
-Uncertain duration of follow up (9 trials): Risk ratio = .89 (95% CI .79-.99; p < .05; I^2 = 40%, i.e., heterogeneity).
A test for differences between the different durations of follow up subgroups was not significant.
Overall progression-free survival (7 trials): HR = .69 (95% CI .58.-.81; p < .0001; I^2 = 45%, i.e., heterogeneity) favouring C-ChRT.
2-year progression-free survival (9 trials): Risk ratio = .91 (95% CI .86-.97; p = .0059; I^2 = 43%, i.e., heterogeneity) favouring C-ChRT.
Overall loco-regional progression-free survival (2 trials): HR = .67 (95% CI .54.-.82; p = .00016; I^2 = 60%, i.e., heterogeneity) favouring C-ChRT.
2-year loco-regional progression-free survival (4 trials): Risk ratio = .84 (95% CI .72-.98; p = .027; I^2 = 59%, i.e., heterogeneity) favouring C-ChRT.
Toxicity
-Treatment-related deaths (14 trials): Risk ratio = 1.38 (95% CI .51-3.73; ns; no heterogeneity).
-Acute pneumonitis (9 trials): Risk ratio = 1.06 (95% CI .58-1.93; ns; no heterogeneity).
-Acute oesophagitis (17 trials): Risk ratio = **1.76 (95% CI 1.34-2.31; p = .000047**; no heterogeneity) favouring RT alone. That is, the risk of acute oesophagitis was 76% higher in the C-ChRT group compared to the RT alone group.
-Pulmonary fibrosis (4 trials): Risk ratio = 1.27 (95% CI .34-4.64; ns; heterogeneity: I^2 = 50%).
-Late oesophagitis (2 trials): Risk ratio = 1.72 (95% CI .32-9.33; ns; I^2 = 23%, i.e., some limited heterogeneity).
-Neutropenia (7 trials): Risk ratio = **3.53 (95% CI 1.84-6.77; p = .00015**; no heterogeneity). That is, the risk of neutropenia was 353% higher in the C-ChRT group compared to the RT alone group.
-Grade 3-4 anaemia (5 trials): **Risk ratio = 4.17 (95% CI 1.13-15.35; p = 032; I^2 = 15%, i.e., limited heterogeneity) favouring RT alone.**
-Grade 1-4 anaemia (9 trials): **Risk ratio = 1.99 (95% CI 1.49-2.64; p < .0001; no heterogeneity).** That is, the risk of

grade1-4 anaemia was 99% higher in the C-ChRT group compared to the RT alone group.

2) C-ChRT versus S-ChRT

Overall Survival (3 trials): HR = **.74 (95% CI .62.-.89; p = .0016; I^2 = 0%, i.e., no heterogeneity**) favouring C-ChRT. That is, C-ChRT is associated with an overall 26% reduction in the risk of death relative to RT alone.

2-year survival:

-5 trials: Risk ratio = .87 (95% CI .78-.97; p < .05; I^2 = 37%, i.e., some heterogeneity) favouring C-ChRT. Absolute survival benefit for C-ChRT = 10% (95% CI -2%- -18%; p = .012; I^2 = 41%, i.e., some heterogeneity)

-RT dose of 50-60 Gy (1 trial): Risk ratio = .76 (95% CI .61-.95; p < .05) favouring C-ChRT.

-RT dose of 60-69.9 Gy (4 trials): Risk ratio = .89 (95% CI .79-1.01; ns; I^2 = 32%, i.e., some heterogeneity).

A test for differences between the low and high dose RT subgroups was not significant.

-Follow up ≥ 22 months (2 trials): Risk ratio = .88 (95% CI .79-.99; p < .05; I^2 = 0%, i.e., no heterogeneity).

-Follow up < 22 months (3 trials): Risk ratio = .84 (95% CI .66-1.06; ns; I^2 = 64%,i.e., heterogeneity).

A test for differences between the different durations of follow up subgroups was not significant.

-Overall progression-free survival (1 trial): HR = .67 (95% CI .3.-1.5; ns).

2-year progression-free survival (2 trials): Risk ratio = .92 (95% CI .78-1.09; ns; I^2 = 69%, i.e., heterogeneity) favouring C-ChRT.

2-year loco-regional progression-free survival (1 trial): Risk ratio = .84 (95% CI .64-1.1, ns).

Toxicity

-Treatment-related deaths (5 trials): Risk ratio = 2.02 (95% CI .9-4.52; ns; no heterogeneity).

-Acute pneumonitis (5 trials): Risk ratio = .99 (95% CI .51-1.91; ns; I^2 = 41%, i.e., heterogeneity).

-Acute oesophagitis (5 trials): Risk ratio = 4.96 (95% CI 2.17-11.37; p < .05; I^2 = 66%, i.e., heterogeneity).

-Neutropenia (5 trials): Risk ratio = 1.18 (95% CI .9-1.55; ns; I^2 = 77%, i.e., heterogeneity).

-Grade 3-4 anaemia (2 trials): Risk ratio = .95 (95% CI .41-2.21; ns; I^2 = 42%, i.e., heterogeneity).

General comments

This Cochrane review is of a high quality with a thorough literature search and assessment of the quality of the included studies. The overall quality of the studies included in both comparison groups appears to be moderate at best. Many of the meta-analyses also reveal heterogeneity between the studies and the results must therefore be interpreted with caution. The evidence provided by this Cochrane Review can therefore only be considered of moderate quality.

References of included studies (for systematic review):

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Citation: Ou,W.; Sun,H.B.; Ye,X.O.; Zhang,B.B.; Yang,H.; Fang,Q.; Li,P.; Wang,S.Y. (2010). Adjuvant Carboplatin-based Chemotherapy in Resected Stage IIIA-N2 Non-small Cell Lung Cancer. Journal of Thoracic Oncology, 5, 1033-1041.

Design: RCT
Country: China

Aim: To assess the effect of vinorelbine/paclitaxel + carboplatin adjuvant chemotherapy compared to observation in patients with completely resected stage IIIA-N2 NSCLC

Inclusion criteria
Patients
-microscopic complete resection ofpathologically proven stage IIIA-N2 NSCLC by lobectomy or pneumonectomy
-aged 18-75
-ECOG performance status of 0-1,
-weight loss < 5%
-adequate bone marrow reserves and adequate liver and renal function

Exclusion criteria
-prior malignancy
-coexisting serious, nonstabilised disease or active uncontrolled infection
-previous chemotherapy, immunotherapy or thoracic radiotherapy
-sleeve or wedge resection
-potentially malignant mediastinal lymph nodes < 1 station or bulky mediastinal lymph nodes before surgery

Population
Chemotherapy: N = 79 (median age 54 years (range 31-73); 56 males; Histology squamous/non-squamous: N = 18/61; T stage T1/T2/T3: N = 8/55/16; N stage metastatic no of LN 1-3 / 4-10 / > 10: N 48/30/1; metastatic level of LN F1/F2/F3: N = 50/26/3; Surgery pneumonectomy/lobectomy: N = 11/68). Chemotherapy regimens vinorelbine + carboplatin / paclitaxel + carboplatin: N = 38 / 41. Median follow up = 35 months (range 1-104 months); 2 patients were lost to follow up.

Observation: N = 71 (median age 59 years (range 24-75); 54 males; Histology squamous/non-squamous: N = 24/47; T stage T1/T2/T3: N = 9/37/25; N stage metastatic no of LN 1-3 / 4-10 / > 10: N 47/23/1; metastatic level of LN F1/F2/F3: N = 55/14/2; Surgery pneumonectomy/lobectomy: N = 17/54). Median follow up = 28 months (range 1-110 months); 3 patients were lost to follow up.
The groups did not differ on any of these variables (all ps ≥ .076)

Interventions
Surgery alone (i.e., Observation) or
Surgery + adjuvant chemotherapy: Chemotherapy began within 28 days of randomisation which was 30 days after surgery and consisted of a 60-min infusion of carboplatin (AUC = 5) and either a 10-minute infusion of 25 mg/m^2 vinorelbine on days 1 and 8 or a 3-hour infusion of 175 mg/m^2 paclitaxel on day 1. Prophylactic granulocyte colony-stimulating factor 2 (G-CSF) supportive therapy was administered after chemotherapy at each cycle on days 2-4 for paclitaxel + carboplatin and on days 9-11 for vinorelbine + carboplatin.
Adjuvant RT after surgery was not permitted.

Outcomes
Survival, disease-free survival, and toxicity

Results *Early closure of the trial after recruitment of 150/260 patients*
Chemotherapy delivery:
-64/79 patients received 4 cycles of full-dose therapy in 12 weeks.
-3/79 patients delayed therapy due to severe toxicity.
-all chemotherapy patients received ≥ 1 dose.
-12/79 patients did not complete 4 cycles of therapy.
-81% of the chemotherapy patients received adjuvant treatment within 2 weeks of randomisation.
-Grade 3-4 toxic events: 19% leukopenia, 41.8% neutropenia, 0% thrombocytopenia, 2.5% anaemia, 2.5% vomiting, 2,5% nausea, 0% diarrhea/fatigue/dental ulcer/dehydration.
Survival:
-3- and 5-year survival rates = 44.6% and 31.1% in the chemotherapy group and 35.4% and 19.1% in the observation group.
-**Median time of survival = 33 (95% CI 27.4-38.6) months and 24 (95% CI 15.8-32.2) months in the chemotherapy and observation groups, respectively (HR = 1.466; 95% CI = 1.017-2.114; p = .037).**
-Multivariate analysis showed that T stage (HR = 1.562, 95% CI 1.146-2.128), postoperative chemotherapy (HR = 1.505, 95% CI 1.04-2.178), and metastatic number of LN (HR = 1.604, 95% CI 1.049-2.453), but not histology or metastatic level of LN were significant predictors of survival.
Disease-free survival:
-Recurrence (all): N = 57 and 51 chemotherapy and observation patients, respectively (p = .97)
-Locoregional recurrence (first site): N = 22 and 15 chemotherapy and observation patients, respectively (p = .34)
-**Distant (excluding brain) recurrence (first site): N = 13 and 20 chemotherapy and observation patients, respectively (p = .035)**
-Brain recurrence (first site): N = 22 and 16 chemotherapy and observation patients, respectively (p = .46)
-3- and 5-year disease-free survival rates = 47.9% and 17.9% in the chemotherapy group and 30.4% and 14.7% in the observation group.
-**Median time of disease-free survival = 32 (95% CI 21.3-42.7) months and 20 (95% CI 13.1-26.9) months in the chemotherapy and observation groups, respectively (HR = 1.56; 95% CI = 1.064-2.287; p = .02).**

General comments
The patients included in this trial were randomised using "simple" (p. 1034) randomisation by a coordinator (no further details provided); it is therefore unclear whether an adequate randomisation procedure and allocation concealment were employed. Furthermore, no blinding (e.g., of assessor of recurrence) appears to have been employed, and the study is likely to be underpowered due to early closure. The evidence provided by this RCT can therefore be considered of low quality.

References of Included Studies: N/A

Citation: Scagliotti,G.V.; Fossati,R.; Torri,V.; Crinò,L.; Giaccone,G.; Silvano,G.; Martelli,M.; Clerici,M.; Cognetti,F.; Tonato,M.; Adjuvant Lung Project Italy/European Organisation for Research Treatment of Cancer-Lung Cancer Cooperative Group Investigators (2003). Randomized study of adjuvant chemotherapy for completely resected stage I, II,

or IIIA non-small-cell Lung cancer. Journal of the National Cancer Institute, 95, 1453-1461.

Design: RCT
Country: European

Aim: To assess the effect of adjuvant mitomycin C + vindesine + cisplatin chemotherapy compared to observation in patients with stage I-IIIA completely resected NSCLC

Inclusion criteria
Patients with
-pathologically proven stage I-IIIA completely resected NSCLC by lobectomy or pneumonectomy, and patients with more limited pathologically complete resections.
-adequate bone marrow reserves, adequate renal and liver function, and a post-operative FEV > 1.2 L/sec

Exclusion criteria
-History of concurrent malignant disease (apart from adequately treated non-melanoma skin cancer or in situ cervical cancer) or other previous primary tumours

Population
Chemotherapy: N = 548 (median age 61 years; 472 males; Pathological stage I/II/IIIA: N = 216/172/160; T status T1/T2/T3: N = 118/345/85; N status N0/N1/N2: N = 257/154/137; Pneumonectomy: N = 134; Complete lymph node dissection: N = 313; Underwent planned RT: N = 238; Histology squamous/adeno/large cell/ bronchoalveolar/NOS: N = 278/196/27/23/24)
Observation: N = 540 (median age 61 years; 465 males; Pathological stage I/II/IIIA: N = 207/183/150; T status T1/T2/T3: N = 100/360/80; N status N0/N1/N2: N = 254/151/135; Pneumonectomy: N = 140; Complete lymph node dissection: N = 290; Underwent planned RT: N = 232; Histology squamous/adeno/large cell/ bronchoalveolar/NOS: N = 262/206/31/20/21)

Interventions
Chemotherapy: Three 3-weekly cycles of mitomycin C 8 mg/m^2 on day 1, vindesine 3 mg/m^2 on days 1 and 8, and 100 mg/m^2 cisplatin on day 1. Dose-adjustments and -delays were allowed, but patients who experienced progression or unacceptable toxicity or who did not received chemotherapy for 6 weeks from the time of last treatment were discontinued from the study.
Post-operative RT (PORT) was optional, prospectively decided and centre-specific. PORT started 3-5 weeks after the last chemotherapy treatment for chemotherapy patients and 4-6 weeks fater surgery for the observation patients. PORT consisted of 50-54 Gy in 2 Gy fractions, 5 times a week over 5-6 weeks.

Outcomes
Survival, progression-free survival, toxicity

Results
Chemotherapy delivery in chemotherapy group:
-350 patients completed the planned 3 cycles, 177 of these had some dose-adjustment or omission of part of the regime (mainly omission of vindesine on day 8).
-110 patients stopped chemotherapy early either due to toxicity or personal choice
-48 patients did not start chemotherapy.
-Median cisplatin, vindesine and mitomycin C actually delivered doses = 96 mg/m^2, 2.8 mg/m^2 and 7.6 mg/m^2
Toxicity:
-Grade 3 and grade 4 neutropenia occurred in 16% and 12%, respectively, of the chemotherapy patients
-Grade 3-4 thrombocytopenia occurred in 5% of the chemotherapy patients
-Grade 2 and grade 3 anaemia occurred in 20% and 2%, respectively, of the chemotherapy patients
-Grade 3 and grade 4 nausea and vomiting occurred in 13% and 4%, respectively, of the chemotherapy patients
-Grade 3 neurotoxicity occurred in 3% of the chemotherapy patients
-Grade 2 ototoxicity occurred in 4% of the chemotherapy patients
PORT delivery:
-N = 117 and 124 in the chemotherapy and observation groups, respectively, completed PORT.
-N = 47 and 16 in the chemotherapy and observation groups, respectively, did not complete PORT as it was interrupted at an early stage.
-No potentially harmful interaction between previous administration of mitomycin C and PORT was reported.
Survival:

-Overall survival: Hazard ratio (HR) = .96; 95% CI = .81-1.13; p = .589). Median survival = 55.2 months in the chemotherapy group and 48 months in the observation group (non-significant)
-No interaction between disease stage and survival was found.
-Overall survival did not differ between the chemotherapy patients receiving all 3 planned cycles of chemotherapy and the observation patients (HR = .86; 95% CI .71-1.04).
-Multivariate analysis indicated that TNM stage (II v I: HR = 2.01; 95% CI 1.62-2.49; III v I: HR = 3.19; 95% CI 2.59-3.93; p < .001) and female gender (HR = 1.33; 95% CI 1.02-1.72; p =.034) were significantly associated with longer survival. Age, tumour histology, type of lymph node dissection (sampling, complete), treatment, and tumour tissue markers (p53, Ki67, K-ras gene mutation) were not significantly associated with survival.
Progression-free survival:
- HR = .89; 95% CI = .76-1.03; p = .128). Median progression-free survival = 36.5 months in the chemotherapy group and 28.9 months in the observation group (non-significant)
-No interaction between disease stage and progression-free survival was found.
-Multivariate analysis indicated that TNM stage (II v I: HR = 1.88; 95% CI 1.54-2.3; III v I: HR = 2.94; 95% CI 2.39-3.53; p < .001) and squamous (versus other) histology (HR = .84; 95% CI .72-.99; p = .037) were significantly associated with longer progression-free survival. Age, gender, type of lymph node dissection (sampling, complete), treatment, and tumour tissue markers (p53, Ki67, K-ras gene mutation) were not significantly associated with progression-free survival.

General comments
The patients included in this trial were centrally randomised with stratification for participating centre, tumour size, lymph node involvement, and intended radiotherapy. No further detail about randomisation procedure or potential allocation concealment are reported, although it is conceivable that central randomisation has gone some way in ensuring allocation concealment. It also appears that no level of blinding (e.g., of assessor of recurrence) was employed. The trial was well-powered and the analyses were conducted on an intention-to-treat basis. Overall, the evidence provided by this RCT can therefore be considered to be of moderate quality.

References of Included Studies: N/A

Citation: Song,W.A.; Zhou,N.K.; Wang,W.; Chu,X.Y.; Liang,C.Y.; Tian,X.D.; Guo,J.T.; Liu,X.; Liu,Y.; Dai,W.M. (2010). Survival Benefit of Neoadjuvant Chemotherapy in Non-small Cell Lung Cancer An Updated Meta-Analysis of 13 Randomized Control Trials. Journal of Thoracic Oncology, 5, 510-516.

Design: Systematic review with meta-analysis
Country: International

Aim: To assess the efficacy of chemotherapy given before surgery in patients with NSCLC

Inclusion criteria
Published (in full or abstract form) RCTs in English or Chinese comparing surgery alone to chemotherapy followed by surgery in adult patients with NSCLC.

Exclusion criteria

Population
13 RCTs with a total of 1637 neoadjuvant chemotherapy patients and 1587 surgery-alone patients. All the trials used platinum-based regimens of neoadjuvant chemotherapy.

Interventions
Neoadjuvant chemotherapy + surgery v surgery alone.

Outcomes
Overall survival

Results
Overall Survival (all patients):
Hazard ratio(HR) = **.84 (95% CI .77-.92; p = .0001; I^2 = 24%, i.e., some limited heterogeneity**) favouring neoadjuvant chemotherapy. That is, neoadjuvant chemotherapy is associated with an overall 16% reduction in the hazard of death relative to surgery alone. These results did not change materially when the trials with the largests weights (HR = .83 (95% CI .75-.93; p = .001; I^2 not reported) or the four Chinese trials (HR = .83 (95% CI .73-.93; p = .002; I^2 not reported) were removed from the analyses

Overall Survival (stage III patients; N = 1586 from 8 trials):
HR = .84 (95% CI .75-.95; p = .005; I^2 = 43%, i.e., heterogeneity) favouring neoadjuvant chemotherapy.

General comments
Although the literature search appears to be thorough and the authors have attempted to address the potential for publication bias, the 13 RCTs included in this systematic review were not of high quality. Consequently, the results must be interpreted with caution, and this point is further underscored by the presence of unexplained heterogeneity in one of the meta-analyses. The evidence provided by this systematic review can therefore only be considered of moderate quality.

References of Included Studies (for systematic review):
-Gilligan,D.; Nicolson,M.; Smith,I.; Groen,H.; Dalesio,O.; Goldstraw,P.; Hatton,M.; Hopwood,P.; Manegold,C.; Schramel,F.; Smit,H.; Van,Meerbeeck J.; Nankivell,M.; Parmar,M.; Pugh,C.; Stephens,R. (2007).
Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. Lancet, 369, 1929-37.
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-Depierre A, Milleron B, Moro-Sibilot D, Chevret S, Quoix E, Lebeau B, et al.Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II and IIIa non-small cell lung cancer. *Journal of Clinical Oncology* 2002; **20** (1):247–53.
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-Pisters K, Vallieres E, Bunn P, Crowley J, Ginsberg R, Ellis P, et al.S9900: A phase III trial of surgery alone or surgery plus pre-operative (pre-op) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Preliminary results. Proceedings of the American Society of Clinical Oncology. 2005; Vol. 24: LBA7012.

Citation: Thomas, M., RüBe, C., Hoffknecht, P., Macha, H. N., Freitag, L., Linder, A. et al. (2008). Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *The lancet oncology, 9,* 636-648.

Design: RCT
Country: Germany

Aim: To assess the efficacy of preoperative cisplatin + etoposide chemotherapy ± concurrent chemoradiation (C-ChRT) in patients with stage IIIA or IIIB NSCLC.

Inclusion criteria
Patients with

-histologically confirmed stage IIIA (T1-3N2M0 or central T3N0-1M0) or IIIB (T4N1-3M0 or T1-4N3M0) NSCLC with assessment of mediastinal lymph nodes by mediastinoscopy (or thoracoscopy/thoracotomy/needle biopsy)
-age < 70 years
-ECOG performance status (PS) = 0 or 1

Exclusion criteria
Patients with T4 tumours with invasion of the heart, oesophagus, or vertebra and patients with malignant pleural/pericardial effusion or involvement of the supraclavicular lymph nodes

Population
C: N = 260 (median age 59 years; 215 males; PS 0/1: N = 227/33; stage T3N0-1M0 / T1-3N2M0 / T4N0-1M0 / T4N2M0 / T1-3N3M0 / T4N3M0: N = 23/70/81/32/44/10; histology squamous/adenosquamous/ adenocarcinoma/ large cell: N = 148/1/101/10); staging by mediastinoscopy: N = 249.
ChRT: N = 264 (median age 59 years; 216 males; PS 0/1: N = 229/35; stage T3N0-1M0 / T1-3N2M0 / T4N0-1M0 / T4N2M0 / T1-3N3M0 / T4N3M0: N = 27/55/78/45/44/15; histology squamous/adenosquamous/ adenocarcinoma/ large cell: N = 135/4/111/14); staging by mediastinoscopy: N = 248.

Interventions
Chemotherapy (C): 3 21-days cycles of cisplatin 55 mg/m^2 on days 1 and 4 + etoposide 100 mg/m^2 on days 1-4. Patients without progressive disease were then randomised to concurrent chemoradiation (C-ChRT) or surgery.
Chemotherapy + ChRT: Chemotherapy as C group. Concurrent ChRT commenced 3-5 weeks after the start of the third cycle of chemotherapy and consisted of 45 Gy in twice-daily fractions of 1.5 Gy with min. 6 hours intervals 5 days/week + carboplatin 100 mg/m^2 + vindesine 3 mg on days 1, 8 and 15 of RT.

All patients: Surgery was scheduled for the C and ChRT groups after completion of the 3rd cycle of chemotherapy and 4-6 weeks after the completion of RT, respectively. C patients who were resected received 54-68.4 Gy of conventionally fractionated RT 4-6 weeks after surgery. Unresectable C patients or C patients who had exploratory thoracotomies started RT (up to 68.4 Gy) as soon as possible. ChRT patients with unresectable tumours or who received exploratory thoracotomies were scheduled to start RT consisting of 24 Gy in twice daily fractions as soon as possible after surgery.

Outcomes
Progression-free survival, overall survival, proportion of patients undergoing surgery

Results
Response:
-C patients: 120/260 responded to the chemotherapy (5 CRs), and 154/260 patients underwent surgery (exploratory thoracotomy rate = 8%)
-ChRT patients: 123/264 responded the chemotherapy (2 CRs), and 131/264 patients responded to ChRT (12 CR). 142/264 patients underwent surgery (exploratory thoracotomy rate = 8%)
-84/260 *(all)* C patients and 98/264 *(all)* ChRT patients received a complete resection (p = .25)
-84/154 C patients and 98/142 ChRT patients *undergoing surgery* received a complete resection (p = .01)
-84/141 C patients and 98/131 ChRT patients *having tumour resection surgery* received a complete resection (p = .008)
-24/84 C patients and 45/98 ChRT patients who received complete resection and achieved mediastinal down staging from N2-3 to N0-1 (p = .02).
-17/84 C patients and 59/98 ChRT patients who received complete resection and had a histopathological response with tumour regression > 90% (p < .0001).
Treatment related deaths in C and ChRT patients respectively:
-During chemotherapy (total N = 3 and 2): Due to sepsis: N = 1 and 1; due to pneumonia: N = 2 and 1.
-During radiotherapy (total N = 5 and 2; p = .2): Due to pneumonitis (54 Gy): N = 2 and 0; due to pneumonitis (68.4 Gy): N = 3 and 0; due to oesophagitis: N = 0 and 1; due to pulmonary haemorrhage: N = 0 and 1.
-During surgery (total N = 7 and 13; p = .11): Due to pneumonia: N = 3 and 4; due to empyema: N = 0 and 1; due to stump insufficiency: N = 1 and 5; due to pulmonary haemorrhage: N = 0 and 2; due to pulmonary embolism: N = 0 and 1, due to heart failure: N = 1 and 0; due to apoplectic stroke: N = 1 and 0: due to mediastinal haemorrhage: N = 1 and 0.
Toxicity in the C and ChRT patients respectively:
-Grade ≥ 3 haematotoxicity: 0.5% and 10% (p < .0001)
-Grade ≥ 3 oesophagitis: N = 4% and 19% (p < .0001)
-Grade ≥ 3 pneumonitis: N = 7% and 1% (p = .0006)
-Surgery complications: 18/154 and 25/142 (p = .15)
Progression-free survival (PFS):

-Median PFS = 10 (95% CI 8.9-11.5) months in the C patients and 9.5 (95% CI 8.3-11.2) months in the ChRT patients (ns). The 1-, 3- and 5-year PFS rates = 41%, 21% and 14% in the C patients and 41%, 20% and 16% in the ChRT patients, respectively (HR = .99, 95% CI .81-1.19, p = .87).
-In patients who had undergone resection and in patients who had had complete resection, PFS did not differ between the groups.
Survival:
-Median survival = 17.6 (95% CI 14.4-20.3) months in the C patients and 15.7 (95% CI 13.4-18) months in the ChRT patients (ns). The 1-, 3- and 5-year survival rates = 63%, 26% and 18% in the C patients and 60%, 28% and 21% in the ChRT patients, respectively (HR = 1, 95% CI .83-1.22, p = .97).
-In patients who had undergone resection and in patients who had had complete resection, survival did not differ between the groups.

General comments
The patients in this study were centrally randomised to treatment group with stratification for stage and centre, and although it is not reported, central randomisation may have gone some way in ensuring allocation concealment. No blinding on any level (e.g., for the assessment of outcomes other than death) was employed. The trial appears to be well-powered to detect potential variations in the primary outcomes and progression-free survival and overall survival analyses were conducted according to the intention-to-treat principle. The evidence provided by this RCT can therefore be considered to be of moderate quality.

References of Included Studies: NA

Citation: Vokes, E. E., Herndon, J. E., Kelley, M. J., Cicchetti, M. G., Ramnath, N., Neill, H. et al. (2007). Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *Journal of clinical oncology, 25,* 1698-1704.

Design: RCT
Country: USA

Aim: To assess the efficacy of induction (I) chemotherapy (C) + concurrent chemoradiation (ChRT) compared to C-ChRT alone in patients with unresectable stage III NSCLC.

Inclusion criteria
Patients with
-histologically/cytologically confirmed untreated unresectable measurable/assessable stage III NSCLC
-N3 disease that can be encompassed in the radiation boost field
-age ≥ 18 years
-CALGB performance status (PS) = 0 or 1
-life expectancy > 2 months
-forced expiratory volume in 1 s > 800 mL

Exclusion criteria
Patients with
-resected tumours
-with scalene/supraclavicular/contralateral hilar lymph node involvement
-direct invasion of the vertebral body
-pleural effusion
-pregnancy

Population
ChRT: N = 182 (median age 63 years; 69% males; PS 0/1/missing: 45% / 52% / 3%; stage IIIA/IIIB/missing: 48% / 46% / 7%; weight loss < 5% / 5-10% / > 10% /missing: 60% / 21% / 9% / 10%).
IC+ChRT: N = 184 (median age 64 years; 63% males; PS 0/1/missing: 44% / 56% / 0%; stage IIIA/IIIB/missing: 49% / 48% / 2%; weight loss < 5% / 5-10% / > 10% /missing: 74% / 13% / 9% / 5%).

Interventions
Concurrent chemoradiation alone (ChRT): Weekly paclitaxel 50 mg/m^2 IV followed by carboplatin AUC 2 IV for 7 weeks. Concurrent chemoradiation consisted of 66 Gy administered in 2 Gy fractions 5 times a week for 7 weeks.

Induction chemotherapy (IC) + ChRT: 2 21-days cycles of IC consisting of paclitaxel 200 mg/m^2 IV followed by carboplatin AUC 6 IV on day 1. For patients without rapid disease progression in other regions than the chest on day 43 IC was followed by concurrent ChRT according to the same schedule as group ChRT alone.

Outcomes
Survival, toxicity

Results
Response:
-IC-ChRT patients: 177/184 patients started IC; 80% recieved 2 cycles and 6% received 1 cycle. 31 (95% CI 25-39)% patients achieved a PR, 39% patients achieved SD and 6% patients progressed. *Response not assessed in 10% patients and data not available inn 14% patients.*
-Overall best response = 67% in the ChRT patients and 61% in the IC-ChRT patients.
Toxicity during concurrent ChRT in the ChRT and IC-ChRT patients respectively:
-Grade 3-4 ANC: 15% and 31% (p < .0001)
-Grade 3-4 WBC: 36% and 44%
-Grade 3-4 HgB: 5% and 12%
-Grade 3-4 lymphopenia: 63% and 58%
-Grade 3-4 febrile neutropenia: 2% and 4%
-Grade 3-4 fatigue: 20% and 21%
-Grade 3-4 anorexia: 20% and 19%
-Grade 3-4 dysphagia-oesophageal: 32% and 36% (ns)
-Grade 3-4 dyspnea: 14% and 19% (ns)
-Grade 3-4 pneumonitis: 4% and 10% (1 fatal event; ns)
-Grade 3-4 maximum toxicity: 84% (G3 = 58%; G4 = 26%) and 85% (G3 = 55%; G4 = 30%; **grade 4; p = .004)**
Survival and progression-free survival (PFS):
-Median survival = 12 and 14 months in the ChRT and IC-ChRT patients, respectively, with 2-, and 3-year survival rates = 29% and 19% in the ChRT patients and 31% and 23% in the IC-ChRT patients, respectively (ns).
-Median PFS = 7 and 8 months in the ChRT and IC-ChRT patients, respectively (p = .2)

General comments
It appears that the patients in this study were centrally randomised to treatment group, but no details are reported of randomisation method or about whether allocation concealment was employed. No blinding on any level (e.g., for the assessment of outcomes other than death) was employed. The trial appears to be well-powered to detect variations in the primary outcomes and progression-free survival and overall survival analyses were conducted according to the intention-to-treat principle. The evidence provided by this RCT can therefore be considered to be of moderate quality, although the lack of methodological detail is a concern.

References of Included Studies: NA

Citation: Waller, D., Peake, M. D., Stephens, R. J., Gower, N. H., Milroy, R., Parmar, M. K., Rudd, R. M. & Spiro, S. G. (2004) Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *European journal of cardio thoracic surgery,* 26: 173-182.

Design: RCT
Country: International

Aim: To assess the effect of surgery (± radiotherapy) + cisplatin-based chemotherapy compared to surgery (± radiotherapy) in patients with stage I-III NSCLC

Inclusion criteria
-histological/cytological diagnosis of NSCLC
-planned to receive (or had recently received) potentially curative surgical resection as part of their primary treatment
-considered fit to received chemotherapy
-no concurrent malignancy or history of malignancy other than non-melanomatous skin cancer within the previous 3 years
-uncertainty about the value of chemotherapy displayed by both doctor and patient

Exclusion criteria

Population
Chemotherapy: N = 192 (median age 61 years; 125 males; Clinical stage I/II/IIIA/IIIB-IV/uncertain: N = 55/71/52/12/2; Histology squamous/adeno/NOS: N = 92/71/29; WHO PS 0/1/2: N = 67/109/16)
Surgery alone: N = 189 (median age 61.9 years; 136 males; Clinical stage I/II/IIIA/IIIB-IV/uncertain: N = 48/74/47/18/2; Histology squamous/adeno/NOS: N = 92/70/27; WHO PS 0/1/2: N = 66/111/12)

Interventions
Chemotherapy choice of the following regimens (decided on a patient-by-patient basis and made before randomisation):
1) MIC: Day 1: Cisplatin 50 mg/m^2, mitomycin 6 mg/m^2, ifosfamide 3 g/m^2.
2) MVP: Day 1: Cisplatin 50 mg/m^2, mitomycin 6 mg/m^2, vinblastine 6 mg/m^2.
3) CV: Day 1: Cisplatin 80 mg/m^2, vindesine 3 mg/m^2; day 8: vindesine 3 mg/m^2.
4) NP: Day 1: Cisplatin 80 mg/m^2, vinorelbine 30 mg/m^2; day 8: vinorelbine 30 mg/m^2.

All the regimens were delivered in three 3-weekly cycles and could be prescribed neo-adjuvantly or adjuvantly, and if radiotherapy was part of the treatment plan, chemotherapy could be given before or after all the primary treatment.

Outcomes
Survival, progression-free survival, toxicity

Results
Treatment choice and delivery:
-368 (97%) patients were randomised in the adjuvant setting
-Radiotherapy was part of the primary treatment in 52 patients (N = 25 in the surgery alone group and N = 27 in the chemotherapy group)
-Chemotherapy regimen: MVP (N = 80), MIC (N = 63), NP (N = 43), CV (N = 6).
-123 patients completed the planned 3 cycles, 77 of these with no dose-adjustments or delays.
-14 patients received 2 cycles, 27 patients received 1 cycle, 25 patients received no chemotherapy, and 3 patients received a different regimen to that originally chosen. In addition, 5 patients allocated to surgery alone received chemotherapy.
-The patients were randomised a median of 42 days after surgery and chemotherapy started a median of 7 days after randomisation in the chemotherapy group.
-No surgery was attempted in 2 patients (both in the chemotherapy group) and 59 patients received incomplete resection (29 patients in the chemotherapy group and 30 patients in the surgery alone group).
Toxicity:
-Grade 3/4 toxicity occurred in 30% of the chemotherapy patients (55% of patients receiving NP, 27% of patients receiving MIC and 17% of patients receiving MVP); mainly haematological (40%), nausea/vomiting (25%), neurological (2%) and renal (6%).
-"There was no evidence that toxicity was related to baseline WHO performance status" (p. 176), but no analyses shown
Survival:
-Overall survival: Hazard ratio (HR) = 1.02; 95% CI = .77-1.35; p = .9). Median survival = 33.9 months in the chemotherapy group and 32.6 months in the surgery alone. 1- and 2-year survival = 74% and 58% in the chemotherapy group and 74% and 60% in the surgery alone patients, respectively.
-**Survival was related to stage (p < .0001),** but not to gender, WHO PS, histology, age, timing of chemotherapy, or to whether primary treatment was surgery alone or surgery + radiotherapy (all ps ≥ .12)
-6 chemotherapy and 1 surgery alone patients died of treatment-related causes.
-Subgroup analyses did not find that any subgroup formed on the basis of age, gender, stage of disease, WHO PS, histology and chosen chemotherapy regimen benefited more or less from chemotherapy.
Progression-free survival:
-HR = .97; 95% CI = .74-1.26; p = .81). Median progression-free survival = 27 months in the chemotherapy group and 24.7 months in the surgery alone. 1- and 2-year progression-free survival = 66% and 53% in the chemotherapy group and 63% and 51% in the surgery alone patients, respectively.

General comments
The patients included in this trial were centrally randomised with stratification for participating centre, choice of chemotherapy regimen, timing of chemotherapy, gender, histology, and performance status. No further detail about randomisation procedure or potential allocation concealment are reported, although it is conceivable that central randomisation has gone some way in ensuring allocation concealment. It also appears that no level of blinding (e.g., of assessor of recurrence) was employed. Although the analyses were conducted on an intention-to-treat basis, the trial

was very under-powered (power = ca. 20%). Overall, the evidence provided by this RCT in isolation can therefore be considered to be of low quality.

References of Included Studies: N/A

Citation: Wang, S.-Y., Ou, W., Lin, Y.-B., Liang, Y., Ye, X., Zhang, B.-B. et al. (2007). A prospective randomized study of adjuvant chemotherapy in completely resected stage III-N2 non small cell lung cancer. *Chinese Journal of Cancer Research., 19,* 189-194.

Design: RCT
Country: China

Aim: To assess the efficacy of adjuvant chemotherapy (compared to surgery alone) in patients with completely resected stage III-N2 NSCLC.

Inclusion criteria
Patients:
-age ≤ 70 years
-performance status (according to which scale not reported) = 0-2
-expected survival > 6 months
-pathologically confirmed NSCLC
-pulmonary lobectomy or pneumonectomy with lymph node dissection
-post-operative pathologic stage IIIA-N2

Exclusion criteria
Patients with
-previous chemotherapy, immunotherapy or thoracic irradiation
-sleeve or wedge resection of tumor
-age > 70 years
-inadequate performance status, pulmonary function test, liver function test, cardiac function test, and renal function test for adjuvant chemotherapy.

Population
Adjuvant chemotherapy (A-Ch): N = 79 (median age 53.9 years; 55 males; T stage T1/T2/T3: N = 3/55/21; N- stage-metastatic number of LN: 1-3/4-10/>10: N = 46/32/1; metastatic level of LN-L1(single lever)/L2/L3 L2 and L3 both multi-lever metastasis): N = 49/27/3; extent of resection: lobectomy/pneumonectomy: N = 67/12; resection type complete/non-completed/post-operative radiation: N = 71/8/8).
Surgery alone (S): N = 71 (median age 60.51 years; 55 males; T stage T1/T2/T3: N = 6/40/25; N- stage-metastatic number of LN: 1-3/4-10/>10: N = 48/22/1; metastatic level of LN-L1/L2/L3: N = 53/15/2; extent of resection: lobectomy/pneumonectomy: N = 55/16; resection type complete/non-completed/post-operative radiation: N = 64/7/7).

The clinical features of the groups did not differ significantly (analyses not presented).

Interventions
A-Ch: Chemotherapy treatment commenced within 30 days of surgery and consisted of four 3-weekly cycles of novelbine (25 mg/m^2) on days 1 and 5 or paclitaxel (175 mg/m^2) on day 1 + carboplatin (AUC = 5) on day 1. "Besides the chemotherapy, 3 weeks later, the incompletely resection patients received regional radiation (40-50 Gy). Surgery alone group received no chemotherapy." (p. 190)

Outcomes
Survival, toxicity.

Results
Chemotherapy delivery & toxicity:
-68/79 patients received 4 cycles of chemotherapy
- N = 0 treatment-related deaths
- Toxicity: Grade 3-4 leucocytopenia = 35%; febrile neutropenia = 2%; vomiting = 56%; nausea = 35%
Survival:
-The 1, 2- and 3-year survival rates = **94.71, 76.28** and 49.62% in the A-Ch group and **88.24, 60.13** and 43.73% in the S group **(ps < .05 for 1- and 2-year survival).** The median survival time = 897 days in the A-Ch group and 821 days in the S

group (p =.0527).
-18/79 A-Ch and 21/71 S patients died of brain metastasis (ns). Although median survival time (812 and 512 days, respectively) did not differ between the treatment groups for these patients, the 2-year survival rates (66.7 and 37.6%, respectively) did differ (p < .05).
-Analysis of prognostic factors: Not prognostic for survival: metastatic number and level of LN, histological type (squamous/non-squamous) and adjuvant chemotherapy (yes/no). **Prognostic: T-stage (odds ratio = 2.052; p = .007 [no further analysis/directional detail reported]); resection type (odds ratio = 2.643; p = .011 [no further analysis/directional detail reported]).**

General comments
Although the patients in this trial were randomised, it is unclear which method of randomisation was used and whether allocation concealment was employed. In addition, there is an absence of detail relating to the analysis section (e.g., confidence intervals) which makes it difficult to fully evaluate the results. The evidence provided by this RCT can therefore be considered of low quality.

References of Included Studies: NA