Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* 1997; 111(6):1710-1717.	Review/Other-Tx	5,319 patients	Revisions in stage grouping of the TNM subsets in the International System for Staging Lung Cancer. Collected database representing clinical, surgical-pathologic, and follow-up information for patients treated for primary lung cancer was analyzed.	The TNM subsets in stage IIIB-T4 any N M0, any T N3M0, and in stage IV any T any N M1, remain the same. Analysis of collected database confirmed the validity of the TNM and stage grouping classification schema.	4
2. van Meerbeeck JP, Surmont VF. Stage IIIA-N2 NSCLC: a review of its treatment approaches and future developments. *Lung Cancer.* 2009; 65(3):257-267.	Review/Other-Tx	N/A	To review the reasons and the biases inherent to the management of patients with stage IIIA-N2 NSCLC and discuss the different treatment approaches with emphasis on survival as evidenced by meta-analyses and large randomized clinical trials. Prospects on novel treatment modalities and future research opportunities are presented.	Radically resected incidental pIIIA-1/2 should be followed by adjuvant chemotherapy whenever appropriate.	4
3. Andre F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 non-small-cell lung cancer: evidence for a subclassification and implications. *J Clin Oncol.* 2000; 18(16):2981-2989.	Observational-Tx	702 patients	To analyze the prognosis of patients with resected N2 NSCLC to propose homogeneous patient subgroups.	The median duration of follow-up was 52 months (range, 18 to 120 months). A multivariate analysis using Cox regression identified four negative prognostic factors, namely, cN2 status (P<. 0001), involvement of multiple lymph node levels (L2+; P<.0001), pT3 to T4 stage (P<.0001), and no preoperative chemotherapy (P<. 01). For patients treated with primary surgery, 5-year survival rates were as follows: mN2, one level involved (mN2L1, n=244): 34%; mN2, multiple level involvement (mN2L2+, n=78): 11%; cN2L1 (n=118): 8%; and cN2L2+ (n=122): 3%. When only patients with mN2L1 disease were considered, the site of lymph node involvement according to the American Thoracic Society numbering system had no prognostic significance (P=.14). Preoperative chemotherapy was associated with a better prognosis for those with cN2 (P<.0001). 5-year survival rates were 18% and 5% for cN2 patients treated with and without preoperative chemotherapy, respectively.	2

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4. Lilenbaum RC, Green MR. Multimodality therapy for non-small-cell lung cancer. *Oncology (Huntingt).* 1994; 8(5):25-31; discussion 32, 35-26.	Review/Other-Tx	N/A	Review several multimodality strategies for NSCLC.	Radiation followed by surgery may increase resectability, but its effects on survival are unproven. Sequential chemotherapy and RT have demonstrated a survival advantage for selected stage III patients. Chemotherapy followed by surgery has shown encouraging results, and additional studies are in progress. Concurrent chemoradiation has shown conflicting results in a few randomized studies. Concurrent chemotherapy and RT followed by surgery has been tested only in phase II trials and further studies are needed.	4
5. Ginsberg RJ. Multimodality therapy for stage IIIA (N2) lung cancer. An overview. *Chest.* 1993; 103(4 Suppl):356S-359S.	Review/Other-Tx	112 patients	Review surgery and postoperative adjuvant chemotherapy or chemoradiation in stage IIIA (N2) lung cancer. Preliminary results of 2 studies were reviewed (9 CRs and 71 PRs in 112 patients).	Of 80 patients who had surgery, complete resection was achieved in 62 (55%). Median survival of 19.5 months for the entire cohort of 112 patients and 27 months for those who had complete resection. 5-year-survival rate is expected to reach 15%.	4
6. van Klaveren RJ, Festen J, Otten HJ, Cox AL, de Graaf R, Lacquet LK. Prognosis of unsuspected but completely resectable N2 non-small cell lung cancer. *Ann Thorac Surg.* 1993; 56(2):300-304.	Observational-Tx	111 patients	To examine prognosis of unsuspected but completely resectable N2 NSCLC. 95/111 patients with NSCLC without clinically evident N2 disease had mediastinoscopy between 1975 and 1985. Mediastinoscopy was positive in 63 cases and negative in 32 cases.	3- and 5-year survival rates were 19% and 10%, respectively. Better survival rate in the operated group due to a better survival of the lobectomy group. No favorable prognostic factors in the nonoperated group, but prognosis improved in the operated group lobectomy and central location. Patients discovered at thoractomy benefit from complete tumor resection and mediastinal lymph node dissection.	2
7. Watanabe Y, Shimizu J, Oda M, Hayashi Y, Watanabe S, Iwa T. Results of surgical treatment in patients with stage IIIA non-small-cell lung cancer. *Thorac Cardiovasc Surg.* 1991; 39(1):44-49.	Observational-Tx	235 stage IIIA NSCLC	To describe results of surgical treatment in patients with stage IIIA NSCLC.	5-year survival rate of the complete resection group was 32%, while that of the incomplete resection group was 5% ($P<0.05$). 5-year survival rate of T3NO-1MO patients with complete resection was 50% and that of T1-2N2MO patients was 30%. Surgical resection may be the treatment of choice whenever complete resection is feasible.	2
8. Goldstraw P, Mannam GC, Kaplan DK, Michail P. Surgical management of non-small-cell lung cancer with ipsilateral mediastinal node metastasis (N2 disease). *J Thorac Cardiovasc Surg.* 1994; 107(1):19-27; discussion 27-18.	Observational-Tx	876 patients	To describe surgical treatment NSCLC with ipsilateral mediastinal node metastasis (N2 disease).	Resection possible in 130 (87.3%) of 149 (patients with unsuspected N2 disease) and complete in 127/149 (85%). Complete follow-up was obtained in 134 patients and the mean follow-up period was 27.25 months. The actuarial 5-year survival for those having complete resection was 20.1%.	2

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9. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer: a review of the current evidence. *Chest.* 2003; 123(1 Suppl):137S-146S.	Review/Other-Dx	N/A	Systematic review to determine the test performance characteristics of CT, PET, MRI, and endoscopic US for staging the mediastinum, and to evaluate the accuracy of the clinical evaluation.	CT: sensitivity, 0.57; specificity, 0.82; PET: sensitivity, 0.84; specificity, 0.89; Endoscopic US: sensitivity, 0.78; specificity, 0.71. PET scanning is more accurate.	4
10. Vansteenkiste JF, De Leyn PR, Deneffe GJ, Lerut TE, Demedts MG. Clinical prognostic factors in surgically treated stage IIIA-N2 non-small cell lung cancer: analysis of the literature. *Lung Cancer.* 1998; 19(1):3-13.	Review/Other-Dx	17 series	Meta-analysis on the prognostic value of several common clinical factors in NSCLC patients with resected N2-disease. Literature data on surgically treated N2-NSCLC-patients from 1980-1995 were analyzed.	Patients with a clinical N0- or N1-status do better. No clear difference between patients undergoing lobectomy or pneumonectomy. Strong evidence that N2-patients with less advanced primary tumor (T-stage) have better prognosis like all operable T-stages (T1 vs T2, T1 vs T3, T2 vs T3).	4
11. Tanoue LT, Detterbeck FC. New TNM classification for non-small-cell lung cancer. *Expert Rev Anticancer Ther.* 2009; 9(4):413-423.	Review/Other-Dx	N/A	To outline the changes in the TNM descriptors and stage groupings anticipated in the official new stage classification system for NSCLC with the forthcoming publication of the 7th Edition of the stage classification.	No results stated in abstract.	4
12. Arriagada R, Auperin A, Burdett S, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet.* 2010; 375(9722):1267-1277.	Review/Other-Tx	2 systematic reviews and meta-analysis	To establish the effects of adding adjuvant chemotherapy to surgery, or to surgery plus RT.	The first meta-analysis of surgery plus chemotherapy vs surgery alone was based on 34 trial comparisons and 8,447 patients (3,323 deaths). The authors recorded a benefit of adding chemotherapy after surgery (HR 0.86, 95% CI, 0.81-0.92, P<0.0001), with an absolute increase in survival of 4% (95% CI, 3-6) at 5 years (from 60% to 64%). The second meta-analysis of surgery plus RT and chemotherapy vs surgery plus RT was based on 13 trial comparisons and 2,660 patients (1,909 deaths). The authors recorded a benefit of adding chemotherapy to surgery plus RT (HR 0.88, 95% CI, 0.81-0.97, P=0.009), representing an absolute improvement in survival of 4% (95% CI, 1-8) at 5 years (from 29% to 33%). In both meta-analyses the authors noted little variation in effect according to the type of chemotherapy, other trial characteristics, or patient subgroup. The addition of adjuvant chemotherapy after surgery for patients with operable NSCLC improves survival, irrespective of whether chemotherapy was adjuvant to surgery alone or adjuvant to surgery plus RT.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
13. Butts CA, Ding K, Seymour L, et al. 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. *J Clin Oncol.* 2010; 28(1):29-34.	Experimental-Tx	482 patients; randomized 240 patients to observation and 242 to adjuvant chemotherapy	To determine whether postoperative chemotherapy conferred a survival benefit in patients on JBR-10. JBR-10 was a phase III randomized trial of adjuvant cisplatin and vinorelbine vs observation in completely resected stage IB or II NSCLC.	Median follow-up was 9.3 years (range, 5.8 to 13.8; 33 lost to follow-up); there were 271 deaths in 482 randomly assigned patients. ACT continues to show a benefit (HR, 0.78; 95% CI, 0.61 to 0.99; P=.04). There was a trend for interaction with disease stage (P=.09; HR for stage II, 0.68; 95% CI, 0.5 to 0.92; P=.01; stage IB, HR, 1.03; 95% CI, 0.7 to 1.52; P=.87). ACT resulted in significantly prolonged disease-specific survival (HR, 0.73; 95% CI, 0.55 to 0.97; P=.03). Observation was associated with significantly higher risk of death from lung cancer (P=.02), with no difference in rates of death from other causes or second primary malignancies between the arms. Prolonged follow-up of patients from the JBR-10 trial continues to show a benefit in survival for adjuvant chemotherapy. This benefit appears to be confined to N1 patients. There was no increase in death from other causes in the chemotherapy arm.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. 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(9):719-727.	Experimental-Tx	840 patients were randomly assigned to observation (n=433) or to 30 mg/m(2) vinorelbine plus 100 mg/m(2) cisplatin (n=407)	To compare the effect of adjuvant vinorelbine plus cisplatin vs observation on survival in patients with completely resected NSCLC.	367 patients in the chemotherapy group and 431 in the control group received their assigned treatment. 301 (36%) patients had stage IB disease, 203 (24%) had stage II disease, and 325 (39%) had stage IIIA disease. Tolerance to chemotherapy mainly included neutropenia in 335 (92%) patients and febrile neutropenia in 34 (9%); seven (2%) toxic deaths were also recorded. Compliance was greater with cisplatin than with vinorelbine (median dose intensity 89% [range 17-108] vs 59% [17-100]). After a median follow-up of 76 months (range 43-116), median survival was 65.7 months (95% CI, 47.9-88.5) in the chemotherapy group and 43.7 (35.7-52.3) months in the observation group. Adjusted risk for death was significantly reduced in patients assigned chemotherapy compared with controls (HR 0.80 [95% CI, 0.66-0.96]; P=0.017). OS at 5 years with chemotherapy improved by 8.6%, which was maintained at 7 years (8.4%). Interpretation: Adjuvant vinorelbine plus cisplatin extends survival in patients with completely resected NSCLC, better defining indication of adjuvant chemotherapy.	1
15. Le Chevalier T. Results of the Randomized International Adjuvant Lung Cancer Trial (IALT): cisplatin-based chemotherapy (CT) vs no CT in 1867 patients (pts) with resected non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol.* 2003; 22:(abstr 6).	Experimental-Tx	1,867 patients (935 for chemotherapy and 932 controls)	Randomized, multicenter trial to evaluate the impact on survival of 3 to 4 cycles of ACT after complete resection of NSCLC. Cisplatin-based chemotherapy was compared with no chemotherapy.	OS: 2 and 5-year survival rates were 70% and 45% in the chemotherapy arm vs 67% and 40% in the control arm respectively (RR=0.86; CI: 0.76-0.98, P<0.03). DFS: 61% and 39% in the chemotherapy arm vs 55% and 34% in the control arm at 2 and 5 years respectively (RR=0.83; CI: 0.74-0.94, P<0.003). Trial supports the use of adjuvant chemotherapy in resected NSCLC.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
16. Le Chevalier T, Dunant A, Arriagada R, et al. Long-term results of the International Adjuvant Lung Cancer Trial (IALT) evaluating adjuvant cisplatin-based chemotherapy in resected non-small cell lung cancer (NSCLC). *J Clin Oncol.* 2008; 26:suppl; abstr 7507.	Experimental-Tx	1,867 patients	Evaluate results of the International Adjuvant Lung Cancer Trial (IALT) study. Patients with completely resected NSCLC were randomly assigned to 3 or 4 cycles of cisplatin-based chemotherapy or to observation.	Median follow-up was 7.5 years at the cut-off date of September 1, 2005. The survival status was known for 1,807 patients. Results showed a beneficial effect of adjuvant chemotherapy on OS (HR: 0.91; 95% CI: 0.81-1.02, P=0.10) and on DFS (HR: 0.88; 95% CI: 0.78-0.98, P=0.02). However, there was a significant difference between the results of OS before and after 5 years (HR: 0.86; CI: 0.76-0.97, P=0.01 vs HR: 1.45; CI: 1.02-2.07, P=0.04); P-value for interaction was 0.006. DFS benefit was also different according to the follow-up duration (P-value for interaction: 0.04; global, first 5 years, HR=0.85, P=0.006; after 5 years, HR=1.33, P=0.16). The analysis of non-lung cancer deaths for the whole period showed a HR of 1.34 (CI: 0.99-1.81; P=0.06).	1
17. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol.* 2008; 26(21):3552-3559.	Review/Other-Tx	5 trials (4,584 patients)	Meta-analysis of lung adjuvant cisplatin evaluation to identify treatment options associated with a higher benefit or groups of patients who benefit from postoperative chemotherapy.	Overall HR of death was 0.89 (95% CI, 0.82 to 0.96; P=.005), corresponding to 5-year absolute benefit of 5.4% from chemotherapy. Chemotherapy effect was higher in patients with better performance status. Postoperative cisplatin-based chemotherapy significantly improves survival in patients with NSCLC.	4
18. 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(19):1453-1461.	Experimental-Tx	1,209 patients: 606 in mitomycin, vindesine and cisplatin group and 603 controls	Adjuvant Lung Project Italy (ALPI), a randomized trial to examine the potential benefits of adjuvant chemotherapy for survival. Stage I, II, IIIA NSCLC after complete resection randomized to 3 cycles of mitomycin, vindesine and cisplatin or no further treatment.	No statistically significant difference between the 2 groups in OS (HR = 0.96, 95% CI 0.81 to 1.13; P=.589) or PFS (HR = 0.89, 95% CI, 0.76 to 1.03; P=.128). Trial failed to confirm the effectiveness of adjuvant chemotherapy for patients with NSCLC.	1
19. 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(25):2589-2597.	Experimental-Tx	482 patients	Randomized trial to determine whether adjuvant vinorelbine plus cisplatin prolongs OS among patients with completely resected early-stage NSCLC. Patients were randomly assigned to vinorelbine plus cisplatin or to observation.	OS was significantly prolonged in the chemotherapy group compared with the observation group (94 vs 73 months. 5-year survival rates were 69 % and 54 %, respectively (P=0.03). Adjuvant vinorelbine plus cisplatin has an acceptable level of toxicity and prolongs DFS and OS among patients with completely resected early-stage NSCLC.	1

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20. Le Pechoux C. Role of postoperative radiotherapy in resected non-small cell lung cancer: a reassessment based on new data. *Oncologist.* 2011; 16(5):672-681.	Review/Other-Tx	N/A	Review role of PORT in patients with resected NSCLC.	Based on the currently available data, PORT should be discussed for fit patients with completely resected NSCLC with N2 nodal involvement, preferably after completion of adjuvant chemotherapy.	4
21. Saynak M, Higginson DS, Morris DE, Marks LB. Current status of postoperative radiation for non-small-cell lung cancer. *Semin Radiat Oncol.* 2010; 20(3):192-200.	Review/Other-Tx	N/A	To review the controversies and rationale for PORT as well as the available data.	The authors recommend PORT for patients with pathologic N2 disease or for patients with close/positive margins or residual macroscopic disease.	4
22. Wagner H, Jr., Lad T, Piantadosi S, Ruckdeschel JC. Randomized phase 2 evaluation of preoperative radiation therapy and preoperative chemotherapy with mitomycin, vinblastine, and cisplatin in patients with technically unresectable stage IIIA and IIIB non-small cell cancer of the lung. LCSG 881. *Chest.* 1994; 106(6 Suppl):348S-354S.	Experimental-Tx	57 patients	Randomized phase II trial that examines preoperative RT and preoperative chemotherapy with mitomycin, vinblastine, and cisplatin in patients with technically unresectable stage IIIA and IIIB NSCLC. Purpose is to evaluate efficacy and toxicity of preoperative treatment programs.	Median survival for group is 12 months, with a 27% actuarial survival at 4 years. Overall toxicity included 2 preoperative toxic deaths and 6 postoperative deaths in 34 patients. Preoperative treatment shows modest efficacy and substantial toxicity.	1
23. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. The Lung Cancer Study Group. *N Engl J Med.* 1986; 315(22):1377-1381.	Experimental-Tx	210 patients	Randomized trial to evaluate effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung.	No evidence that RT improved survival. Overall recurrence rates were reduced by RT in patients with N2 disease ($P<0.05$). RT can reduce local recurrences after resection of epidermoid carcinoma of the lung, but does not increase survival rates.	1
24. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet.* 1998; 352(9124):257-263.	Review/Other-Tx	2,128 patients from 9 randomized trials	Systematic review and meta-analysis of randomized trials to determine role of PORT in the treatment of patients with completely resected NSCLC.	Results show a significant adverse effect of PORT on survival (HR 1.21 [95% CI, 1.08-1.34]). 21% relative increase in the risk of death is equivalent to an absolute detriment of 7% (3-11) at 2 years, reducing OS from 55% to 48%. Subgroup analyses suggest that this adverse effect was greatest for patients with stage I/II, N0-N1 disease, whereas for those with stage III, N2 disease there was no clear evidence of an adverse effect. PORT is detrimental to patients with early-stage completely resected NSCLC and should not be used routinely for such patients.	4

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25. Emami B, Kaiser L, Simpson J, Shapiro S, Roper C, Lockett MA. Postoperative radiation therapy in non-small cell lung cancer. *Am J Clin Oncol.* 1997; 20(5):441-448.	Observational-Tx	173 patients	Patients with diagnosis of NSCLC were treated with surgery and PORT. All patients were retrospectively reviewed and restaged according to the new American Joint Committee (AJC) staging classification.	Indications for PORT were positive surgical margins (32 patients), metastatic hilar nodes (78 patients), and metastatic mediastinal nodes (62 patients). Locoregional control for stages I, II, and IIIA was 85%, 75%, and 85%, respectively. 5-year actuarial survival was 35% for stage I and 20% for stages II and IIIA. Patients with N0 disease (positive margins) had 5-year survival of 25%, while patients with N1 and N2 disease had a 5-year survival of 20%.	2
26. Sawyer TE, Bonner JA, Gould PM, et al. Effectiveness of postoperative irradiation in stage IIIA non-small cell lung cancer according to regression tree analyses of recurrence risks. *Ann Thorac Surg.* 1997; 64(5):1402-1407; discussion 1407-1408.	Observational-Tx	224 patients	To determine the effectiveness of PORT in stage IIIA NSCLC according to regression tree analyses of recurrence risks. Regression tree analysis was used to separate patients who had undergone operation alone into groups that had a high, intermediate, or low risk of local recurrence and death.	The use of adjuvant PORT (compared with operation alone) was associated with an improvement in freedom from local recurrence and survival for patients who had an intermediate or high risk of local recurrence and death. However, the greatest level of improvement in freedom from local recurrence ($P<0.0001$) and survival ($P=0.0002$) associated with the use of adjuvant PORT was in the high-risk group. Similarly, but of lesser magnitude, the intermediate-risk group had improved freedom from local recurrence and survival rates with the use of adjuvant PORT ($P=0.002$ and $P=0.01$, respectively). For the low-risk group, the freedom from local recurrence and survival rates were not statistically different between the patients who received adjuvant PORT and those who underwent observation.	2
27. Logan DM, Lochrin CA, Darling G, Eady A, Newman TE, Evans WK. Adjuvant radiotherapy and chemotherapy for stage II or IIIA non-small-cell lung cancer after complete resection. Provincial Lung Cancer Disease Site Group. *Cancer Prev Control.* 1997; 1(5):366-378.	Review/Other-Tx	N/A	Guidelines on the use of PORT and chemotherapy in the treatment of patients with completely resected stage II or IIIA NSCLC.	Evidence from randomized controlled trials show that PORT reduces rates of local recurrence by 11%-18% (or 1.6-19-fold). RT is recommended if outcome of interest is a reduction in the frequency of local tumor recurrence. There is no evidence of a survival benefit from PORT alone.	4
28. Wagner H, Jr. Postoperative radiation therapy for patients who have resected non-small cell lung cancer. *Hematol Oncol Clin North Am,* 2005; 19(2):283-302, vi.	Review/Other-Tx	N/A	Article addresses the potential roles of local and systemic adjuvant therapies for patients who have resected lung cancer, reviews the data of completed clinical trials, and suggests strategies for future investigations.	Older retrospective series reported that PORT of mediastinal and hilar nodes improved survival in patients who had resected NSCLC, particularly if they had nodal metastases.	4

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29. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol.* 2006; 24(19):2998-3006.	Observational-Tx	7,465 patients	Retrospective study to examine the association between survival and PORT in patients with resected NSCLC. Patients were selected from the Surveillance, Epidemiology, and End Results database.	PORT did not have a significant impact on survival, but for patients with N2 nodal disease, PORT was associated with a significant increase in survival. For patients with N0 (HR = 1.176; 95% CI, 1.005 to 1.376; P=.0435) and N1 (HR = 1.097; 95% CI, 1.015 to 1.186; P=.0196) nodal disease, PORT was associated with a significant decrease in survival.	2
30. Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P, Mahe MA. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys.* 2008; 72(3):695-701.	Observational-Tx	232 patients received PORT	To study the impact of PORT on survival in the Adjuvant Navelbine International Trialist Association (ANITA) randomized study of adjuvant chemotherapy.	Overall, 232 of 840 patients received PORT (33.3% in the observation arm and 21.6% in the chemotherapy arm). In univariate analysis, PORT had a deleterious effect on the overall population survival. Patients with pN1 disease had an improved survival from PORT in the observation arm (median survival 25.9 vs 50.2 months), whereas PORT had a detrimental effect in the chemotherapy group (median survival 93.6 months and 46.6 months). In contrast, survival was improved in patients with pN2 disease who received PORT, both in the chemotherapy (median survival 23.8 vs 47.4 months) and observation arm (median 12.7 vs 22.7 months).	2
31. Higgins KA, Chino JP, Berry M, et al. Local failure in resected N1 lung cancer: implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys.* 2012; 83(2):727-733.	Observational-Tx	198 patients	To evaluate actuarial rates of local failure in patients with pathologic N1 NSCLC and to identify clinical and pathologic factors associated with an increased risk of local failure after resection.	Among 1,559 patients who underwent surgery during the time interval, 198 met the inclusion criteria. Of these patients, 50 (25%) received adjuvant chemotherapy. Actuarial (5-year) rates of local failure, distant failure, and OS were 40%, 55%, and 33%, respectively. On multivariate analysis, factors associated with an increased risk of local failure included a video-assisted thoracoscopic surgery approach (HR, 2.5; P=0.01), visceral pleural invasion (HR, 2.1; P=0.04), and increasing number of positive N1 lymph nodes (HR, 1.3 per involved lymph node; P=0.02). Chemotherapy was associated with a trend toward decreased risk of local failure that was not statistically significant (HR, 0.61; P=0.2).	2

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32. Varlotto JM, Medford-Davis LN, Recht A, Flickinger JC, Schaefer E, DeCamp MM. Failure rates and patterns of recurrence in patients with resected N1 non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011; 81(2):353-359.	Observational-Tx	60 patients	To examine the local and distant recurrence rates and patterns of failure in patients undergoing potentially curative resection of N1 NSCLC.	Local and distant failure rates (as the first site of failure) at 2, 3, and 5 years were 33%, 33%, and 46%; and 26%, 26%, and 32%, respectively. The most common site of local failure was in the mediastinum; 12 of 18 local recurrences would have been included within proposed PORT fields. Patients who received chemotherapy were found to be at increased risk of local failure, whereas those who underwent pneumonectomy or who had more positive nodes had significantly increased risks of distant failure.	2
33. Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. *Int J Radiat Oncol Biol Phys.* 2006; 65(4):1097-1105.	Review/Other-Tx	61 patients	To analyze local-regional patterns of failure after surgical resection of NSCLC.	All patients had CT imaging for review, and 54% also had PET imaging. The median number of local-regional recurrent sites was two (range, 1-6). For all patients, the most common site of failure was the bronchial stump/staple line (44%), which was present more often in those who had a wedge resection than in those who had a more radical procedure (79% vs 34%, P=0.005). Patients with initial nodal involvement (pN1-2) were not more likely to have involvement of the mediastinum than were patients with pN0 disease (64% vs 72%, P=0.72), but were more likely to have involvement of the supraclavicular fossa (27% vs 4%, P=0.04). Mediastinal involvement, without overt evidence of hilar involvement, occurred in 59% of patients. Left-sided tumors tended to involve the contralateral mediastinum more frequently than did right-sided tumors. Patterns of failure after resection are diagrammed and follow a fairly predictable pattern on the basis of involved lobe.	4
34. Chetty IJ, Curran B, Cygler JE, et al. Report of the AAPM Task Group No. 105: Issues associated with clinical implementation of Monte Carlo-based photon and electron external beam treatment planning. *Med Phys.* 2007;34(12):4818-4853.	Review/Other-Tx	N/A	A preliminary report to review the tenets of the MC method and to provide the framework upon which to build a comprehensive program for commissioning and routine quality assurance of MC-based treatment planning systems.	No results stated in abstract.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Xiao Y, Papiez L, Paulus R, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2009;73(4):1235-1242.	Observational-Tx	20 patients	To determine the dose prescription and critical structure constraints for future SBRT lung protocols that mandate density-corrected dose calculations.	With heterogeneity corrections applied, the planning target volume receiving >/=60 Gy decreased, on average, 10.1% (standard error, 2.7%) from 95% (p = .001). The maximal dose to any point >/=2 cm away from the planning target volume increased from 35.2 Gy (standard error, 1.7) to 38.5 Gy (standard error, 2.2).	3
36. Bradley J. A Randomized Phase III Comparison of Standard- Dose (60 Gy) Versus Highdose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab (IND #103444) in Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0617. Accessed 9 May 2013.	Review/Other-Tx	ongoing	To compare the OS of patients treated with high-dose versus standard-dose conformal radiation therapy in the setting of concurrent chemotherapy; To compare the OS of patients treated with cetuximab versus without cetuximab in the setting of concurrent chemotherapy. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0617	This trial is still recruiting study subjects and results are not available yet.	4
37. Bezjak A. Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0813. Accessed 9 May 2013.	Review/Other-Tx	ongoing	Phase I Portion: To determine the maximal tolerated dose of SBRT for centrally-located NSCLC and the efficacy of that dose in patients who are not operative candidates. Phase II Portion: To estimate the primary tumor control rate at the maximal tolerated dose of SBRT. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0813	This trial is still recruiting study subjects and results are not available yet.	4
38. Videtic GMM. A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0915. Accessed 9 May 2013.	Review/Other-Tx	ongoing	To determine the rate of 1-year grade 3 or higher adverse events definitely, probably, or possibly related to treatment. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0915	This trial is still recruiting study subjects and results are not available yet.	4
39. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys.* 2010;37(8):4078-4101.	Review/Other-Tx	N/A	A review of the literature to identify reported clinical findings and expected outcomes for SBRT.	No results stated in abstract.	4

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Altorki NK, Keresztes RS, Port JL, et al. Celecoxib, a selective cyclo-oxygenase-2 inhibitor, enhances the response to preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer. *J Clin Oncol.* 2003; 21(14):2645-2650.	Observational-Tx	29 patients	Phase II trial in which patients with stages IB to IIIA NSCLC were treated with two preoperative cycles of paclitaxel and carboplatin, as well as daily celecoxib, followed by surgical resection.	The overall clinical response rate was 65% (48% with PR; 17% with clinical response). 28 patients were explored and underwent complete resection. There were no path clinical responses, but 7 (24%) had minimal residual microscopic disease.	3
41. Andre F, Grunenwald D, Pujol JL, et al. Patterns of relapse of N2 nonsmall-cell lung carcinoma patients treated with preoperative chemotherapy: should prophylactic cranial irradiation be reconsidered? *Cancer.* 2001; 91(12):2394-2400.	Observational-Tx	81 treated with preoperative chemotherapy and 186 treated with primary surgery	Compared patterns of relapse in clinically detectable N2 NSCLC (IIIA) treated with preoperative chemotherapy with the relapse patterns of comparable patients who had been treated with primary surgery.	Overall 20% of patients developed a LRR. Chemotherapy decreased the risk of visceral metastasis as 28% of the patients preoperatively treated and 38% of those not treated with preoperative chemotherapy presented a visceral metastasis ($P<0.05$). Preoperative chemotherapy and adenocarcinoma subtypes were associated with a higher rate of brain metastasis ($P<0.05$). 32% of the patients treated preoperatively and 18% of those not treated with preoperative chemotherapy presented a brain metastasis ($P<0.05$), which was isolated in 22% and 11% of the patients, respectively ($P<0.05$).	2
42. Betticher DC, Hsu Schmitz SF, Totsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. *J Clin Oncol.* 2003; 21(9):1752-1759.	Observational-Tx	90 patients	Multicenter, phase II trial to examine the efficacy and toxicity of neoadjuvant docetaxel-cisplatin with subsequent surgical resection in locally advanced NSCLC.	Overall response rate was 66%. 75 underwent tumor resection. Path CR in 19. Downstaging to N0-1 at surgery prognostic: prolonged event-free survival and OS. Median event-free survival and OS 14.8 months and 33 months. Local relapse occurred in 27% and distant metastases in 37%. Mediastinal clearance and complete resection prognostic for increased survival.	2

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
43. Cappuzzo F, De Marinis F, Nelli F, et al. Phase II study of gemcitabine-cisplatin-paclitaxel triplet as induction chemotherapy in inoperable, locally-advanced non-small cell lung cancer. *Lung Cancer.* 2003; 42(3):355-361.	Observational-Tx	42 patients	Phase II study to determine the response rate, surgical resectability, and tolerability of gemcitabine-cisplatin-paclitaxel triplet as induction chemotherapy in inoperable, locally-advanced NSCLC.	Grade 3-4 neutropenia was the main hematologic toxicity, occurring in 28% of patients. Grade 3-4 thrombocytopenia was observed in only 11% of cases. No neutropenic fever or bleeding episodes were recorded. Severe non-hematologic toxicity was uncommon. 30 (71%, 95% CI: 57.2%-84.7%) of the 42 eligible patients had objective responses (1 complete and 29 PRs). After induction chemotherapy, 21 patients (50%) went to surgery. Complete resection was obtained in 16 patients (38%). Viable tumor was present in 18/21 resection specimens. In 3 cases only necrotic tumor cells were identified, for a pathological CR of 7%. With a median follow-up of 13.9 months, median time to progression was 17.4 months, median survival 21.7 months and estimated 1-year survival 92%.	2
44. Cappuzzo F, Selvaggi G, Gregorc V, et al. Gemcitabine and cisplatin as induction chemotherapy for patients with unresectable Stage IIIA-bulky N2 and Stage IIIB nonsmall cell lung carcinoma: an Italian Lung Cancer Project Observational Study. *Cancer.* 2003; 98(1):128-134.	Observational-Tx	129 consecutive patients	To evaluate the activity and safety of gemcitabine and cisplatin as a neoadjuvant regimen in patients with unresectable stage IIIA-bulky N2 and stage IIIB NSCLC.	62% PR, 33% stable disease, and 5% had disease progression during chemotherapy. 31% considered resectable and underwent thoracotomy. Complete resectability in 29%, with 2% achieving a pathologic CR. After surgery, some received definitive adjuvant RT. Median survival 19.4 months, 1-year survival 74%.	2
45. Date H, Kiura K, Ueoka H, et al. Preoperative induction chemotherapy with cisplatin and irinotecan for pathological N(2) non-small cell lung cancer. *Br J Cancer.* 2002; 86(4):530-533.	Observational-Tx	15 patients	Phase I/II study to determine whether the surgical resection after induction chemotherapy with cisplatin and irinotecan was feasible and could improve the treatment outcome for patients with pathological N2 NSCLC.	Objective response rate was 73%. Complete resection was achieved in 73%. The 5-year survival rate was 40% for all the 15 patients and it was 55% for the 11 patients who underwent complete resection.	2
46. De Candis D, Stani SC, Bidoli P, et al. Induction chemotherapy with carboplatin/paclitaxel followed by surgery or standard radiotherapy and concurrent daily low-dose cisplatin for locally advanced non-small cell lung cancer (NSCLC). *Am J Clin Oncol.* 2003; 26(3):265-269.	Observational-Tx	43 patients	Phase II study to examine the efficacy of carboplatin/paclitaxel followed by surgery or standard RT and concurrent daily low-dose cisplatin for locally advanced NSCLC.	Of 42 evaluable patients 38% achieved PR and 7% CR for an overall response rate of 45%. R0 resectability rate was 29%, with 21% pathologic CR. 3 CR with concurrent chemoradiotherapy in responsive but unresected patients. Median survival: 15 months. 1-year and 2-year survival rates were 51% and 22%. The median survival in the responsive resected patients was 26 months, with 2-year survival of 57%.	1

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. Maurel J, Martinez-Trufero J, Artal A, et al. Prognostic impact of bulky mediastinal lymph nodes (N2>2.5 cm) in patients with locally advanced non-small-cell lung cancer (LA-NSCLC) treated with platinum-based induction chemotherapy. *Lung Cancer.* 2000; 30(2):107-116.	Observational-Tx	70 patients	To retrospectively determine whether pretreatment clinical characteristics in patients with locally advanced NSCLC treated with platinum-based induction chemotherapy regimens were predictors of response or survival.	The overall response rate to induction chemotherapy was 40%. Median survival of the 70 patients was 13 months, with a 4-year survival of 15%.	2
48. Santo A, Pedersini R, Pasini F, et al. A phase II study of induction chemotherapy with gemcitabine (G) and cisplatin (P) in locally advanced non-small cell lung cancer: interim analysis. *Lung Cancer.* 2001; 34 Suppl 4:S15-20.	Observational-Tx	47 patients	Phase II study to evaluate the activity and toxicity of the Gemcitabine-cisplatin regimen (3 cycles: Gemcitabine 1250 mg/m (2) IV on days 1 and 8, and cisplatin 100 mg/m (2) on day 8 every 3 weeks) in locally advanced NSCLC.	CR 5.2%, PR 61.5%, stable disease 20.5%, and progressing disease 12.8%. Among the 16 resected patients, a radical complete resection was possible in 81.3%, tumor downstaging was observed in 56.2%.	2
49. Scinto AF, Ferraresi V, Milella M, et al. Ifosfamide, cisplatin and etoposide combination in locally advanced inoperable non-small-cell lung cancer: a phase II study. *Br J Cancer.* 1999; 81(6):1031-1036.	Observational-Tx	43 patients	Phase II study to examine the toxicity and activity of ifosfamide, cisplatin and etoposide combination as initial treatment for locally advanced inoperable NSCLC.	Overall response rate after 3 chemotherapy courses was 69% (1 CR). 10 patients (8/10 patients in stage IIIA, 2/33 patients in stage IIIB) underwent radical surgery. Median time to progression for patients not undergoing surgery was 8 months; median DFS for patients rendered not evaluable by surgery was 26 months. Median OS for the entire group was 12.5 months (range 2-57+).	2
50. Takita H, Pitoniak RF. Induction chemotherapy for locoregional lung cancer using paclitaxel combination. A preliminary report. *J Exp Clin Cancer Res.* 2000; 19(3):291-293.	Observational-Tx	38 patients	A preliminary report on induction chemotherapy for locoregional lung cancer using paclitaxel combination.	Overall response rate of 74%. The response rate for 14 resectable patients (stage I and II) was 86%.	3
51. Torre W, Sierra A. Postoperative complications of lung resection after induction chemotherapy using Paclitaxel (and radiotherapy) for advanced non-small lung cancer. *J Cardiovasc Surg (Torino).* 2002; 43(4):539-544.	Review/Other-Tx	19 patients	To determine whether the postoperative course of locally advanced NSCLC can be influenced by preoperative chemotherapy.	Complications occurred in the immediate postoperative period in 9 patients: 1 postpneumonectomy respiratory distress syndrome, 2 bronchopleural fistulae, 4 prolonged air leaks, one complete dehiscence of the thoracotomy scar and one colitis caused by anaerobes. Surgery for NSCLC has to be considered a high-risk procedure. Further studies needed to define exact role of therapeutic measures.	4

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
52. Yang CH, Tsai CM, Wang LS, et al. Gemcitabine and cisplatin in a multimodality treatment for locally advanced non-small cell lung cancer. *Br J Cancer.* 2002; 86(2):190-195.	Observational-Tx	52 patients	Phase II study to test the feasibility of using gemcitabine and cisplatin before local treatment for stage III NSCLC patients. Patients had 3 cycles of induction gemcitabine (1000 mg/m (-2), days 1, 8, 15) and cisplatin (90 mg/m (-2), day 15) every 4 weeks before evaluation for operability.	69% were operable. 35% had their tumors completely resected. 2 patients had pathological CR. Median OS 19.1 months, projected 1-year survival was 66% and 2-year survival was 34%.	2
53. Sugarbaker DJ, Herndon J, Kohman LJ, Krasna MJ, Green MR. Results of cancer and leukemia group B protocol 8935. A multiinstitutional phase II trimodality trial for stage IIIA (N2) non-small-cell lung cancer. Cancer and Leukemia Group B Thoracic Surgery Group. *J Thorac Cardiovasc Surg.* 1995; 109(3):473-483; discussion 483-475.	Observational-Tx	74 patients	To assess the feasibility, efficacy, and toxicity of neoadjuvant chemotherapy and postoperative, sequential chemotherapy and thoracic RT in the treatment of patients with pathologically confirmed stage IIIA (N2) NSCLC.	OS at 3 years was 23%. Patients undergoing resection had significantly improved survival at 3 years compared with patients not having resection: 46% for complete resection (median 20.9 months), 25% for incomplete resection (median 17.8 months), and 0% for no resection (median 8.5 months). 5 deaths occurred during the treatment period. A total of 18 of the 46 (39%) patients who underwent resection are either alive, and disease-free or have died without recurrence.	1
54. Depierre A, Milleron B, Moro-Sibilot D, 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. *J Clin Oncol.* 2002; 20(1):247-253.	Experimental-Tx	355 patients	Randomized, phase III trial to examine whether preoperative chemotherapy could improve survival in resectable stage I (except T1N0), II, and IIIA NSCLC. Compared 2 cycles of mitomycin (6 mg/m(2), day 1), ifosfamide (1.5 g/m(2), days 1 to 3) and cisplatin (30 mg/m(2), days 1 to 3), and two additional postoperative cycles for responding patients to primary surgery. In both arms, patients with pT3 or pN2 disease received thoracic RT.	Median survival: 37 months for induction chemo and 26.0 months for surgery alone (P=.15). After a nonsignificant excess of deaths during treatment, the effect of chemotherapy was significantly favorable on survival (RR, 0.74; P=.044). DFS longer in chemotherapy arm (P=.033).	1

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
55. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med.* 1994; 330(3):153-158.	Experimental-Tx	60 patients	Randomized trial comparing preoperative chemotherapy plus surgery with surgery alone to examine the possible benefit of preoperative chemotherapy and surgery for the treatment of patients with NSCLC.	The median period of survival was 26 months in the patients treated with chemotherapy plus surgery, as compared with 8 months in the patients treated with surgery alone (P<0.001); the median period of DFS was 20 months in the former group, as compared with 5 months in the latter (P<0.001). The rate of recurrence was 56% in the group treated with chemotherapy plus surgery and 74% in the group treated with surgery alone. The prevalence of mutated K-ras oncogenes was 15% among the patients receiving preoperative chemotherapy and 42% among those treated with surgery alone (P=0.05). Most of the patients treated with chemotherapy plus surgery had tumors that consisted of diploid cells, whereas the patients treated with surgery alone had tumors with aneuploid cells.	1
56. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst.* 1994; 86(9):673-680.	Experimental-Tx	60 patients	Prospective, randomized study to compare the results of perioperative chemotherapy and surgery with those of surgery alone in patients with previously untreated, potentially resectable clinical stage IIIA NSCLC.	Median survival of 64 months for patients treated with perioperative chemotherapy and surgery compared with 11 months for patients who had surgery alone (P<.008 by log-rank test; P<.018 by Wilcoxon test). Estimated 2- and 3-year survival rates were 60% and 56% for the perioperative chemotherapy patients and 25% and 15% for those who had surgery alone, respectively. Treatment strategy using perioperative chemotherapy and surgery was more effective than surgery alone.	1

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
57. Pisters K, Vallieres E, Bunn PA, et al. S9900: Surgery alone or surgery plus induction (ind) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Follow-up on a phase III trial. *J Clin Oncol., 2007 ASCO Annual Meeting Proceedings Part I.* 2007; 25(18s):7520.	Experimental-Tx	354 patients	Follow-up on a phase III trial to determine if induction paclitaxel/carboplatin could improve survival over surgery alone.	S9900 closed 07/04 when adjuvant chemotherapy became standard. 354 patients had accrued; 174-surgery alone, 180-induction paclitaxel/carboplatin; 19 were ineligible. Median age 65 years, 66% male, 70% IB/IIA, 30% IIB/IIIA. Major radiographic response to induction paclitaxel/carboplatin was 41%. Treatment-related deaths: 3 during induction paclitaxel/carboplatin, 11 within 30 days of surgery (7-induction paclitaxel/carboplatin arm, 4-control). PFS, OS rates and HRs are shown. PFS and OS continue to trend in favor of induction paclitaxel/carboplatin with HRs similar to those observed in adjuvant trials, supporting the role of chemotherapy in operable NSCLC.	1
58. Gilligan D, Nicolson M, Smith I, et al. 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.* 2007; 369(9577):1929-1937.	Experimental-Tx	519 patients	Multicenter, randomized trial to determine whether outcomes could be improved by giving platinum-based chemotherapy before surgery in patients with operable NSCLC of any stage.	Neo-adjuvant chemotherapy was feasible (75% of patients received all 3 cycles of chemotherapy), resulted in good response rate (49% [95% CI, 43%-55%]) and down-staging in 31% (25%-37%) of patients, and did not alter the type or completeness of the surgery. Updating the systematic review by addition of the present result suggests a 12% relative survival benefit with the addition of neoadjuvant chemotherapy, equivalent to an absolute improvement in survival of 5% at 5 years.	1
59. Scagliotti GV, Pastorino U, Vansteenkiste J, et al. A phase III randomized study of surgery alone or surgery plus preoperative gemcitabine-cisplatin in early-stage non-small cell lung cancer (NSCLC): Follow-up data of Ch.E.S.T. *J Clin Oncol.* 2008; 26:suppl; abstr 7508.	Experimental-Tx	270 patients; 141 randomized to surgery alone and 129 to gemcitabine-cisplatin plus surgery	Phase III randomized study to determine whether 3 preoperative cycles of gemcitabine-cisplatin followed by radical surgery provides a reduction in the risk of progression compared with surgery alone in patients with stage IB- IIIA NSCLC.	3-year PFS rate was 48% in surgery (95% CI, 38%-56%) and 53% in q3week followed by surgery (95% CI, 43%-61%) (P=0.11, log-rank test). The overall 3-year survival rate was 60% in surgery (95% CI, 51%-68%) and 67% in q3week followed by surgery (95% CI, 58%-75%) (P=0.053). Study indicates the efficacy outcome estimates in the range of those reported from other neoadjuvant trials in the same setting of patients.	1

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
60. Berghmans T, Paesmans M, Meert AP, et al. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. *Lung Cancer.* 2005; 49(1):13-23.	Review/Other-Tx	25 studies	An updated meta-analysis on the survival improvement in resectable NSCLC with (neo) adjuvant chemotherapy.	Meta-analysis showed HR of the combined results was 0.66 (95% CI, 0.48-0.93) in favor of the addition of induction chemotherapy to a standard surgical procedure and 0.84 (95% CI, 0.78-0.89) in favor of adjuvant chemotherapy. Meta-analysis shows the efficacy of adjuvant chemotherapy in stages I and II resected NSCLC. More data needed to confirm role for induction chemotherapy.	4
61. Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *J Thorac Oncol.* 2006; 1(7):611-621.	Review/Other-Tx	7 randomized controlled trials, 988 patients	Systematic review and meta-analysis to assess the effectiveness of preoperative chemotherapy in NSCLC.	Preoperative chemotherapy improved survival with a HR of 0.82 (95% CI, 0.69-0.97; P=0.02). This is equivalent to an absolute benefit of 6%, increasing OS across all stages of disease from 14%-20% at 5 years. No evidence of statistical heterogeneity. Analysis did not address important questions.	4
62. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst.* 2007; 99(6):442-450.	Experimental-Tx	579 patients; 167 patients allocated to resection and 165 to RT	Large multicenter prospective randomized trial to compare surgery with RT in patients with stage IIIA-N2 NSCLC who showed a response to induction chemotherapy.	Induction chemotherapy resulted in a response rate of 61% (95% CI, 57% to 65%) among the 579 eligible patients. A total of 167 patients were allocated to resection and 165 to RT. Of the 154 (92%) patients who underwent surgery, 14% had an exploratory thoracotomy, 50% a radical resection, 42% a pathologic downstaging, and 5% a pathologic CR; 4% died after surgery. PORT was administered to 62 (40%) of patients in the surgery arm. Among the 154 (93%) irradiated patients, overall compliance to the RT prescription was 55%, and grade 3/4 acute and late esophageal and pulmonary toxic effects occurred in 4% and 7%; one patient died of radiation pneumonitis. Median and 5-year OS for patients randomly assigned to resection vs RT were 16.4 vs 17.5 months and 15.7% vs 14%, respectively (HR = 1.06, 95% CI, 0.84 to 1.35). Rates of PFS were also similar in both groups.	1

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
63. Shah AA, Berry MF, Tzao C, et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. *Ann Thorac Surg.* 2012; 93(6):1807-1812.	Review/Other-Tx	7 studies	Systematic review and meta-analysis were performed to test the hypothesis that the addition of RT to induction chemotherapy prior to surgical resection does not improve survival compared with induction chemotherapy alone.	7 studies met criteria for analysis, including 1 randomized control trial, 1 phase II study, 3 retrospective reviews, and 2 published abstracts of randomized controlled trials. None of the studies demonstrated a survival benefit to adding induction radiation to induction chemotherapy vs induction chemotherapy alone. The meta-analysis performed on randomized studies (n=156 patients) demonstrated no benefit in survival from adding radiation (HR 0.93, 95% CI, 0.54 to 1.62, P=0.81), nor did the meta-analysis performed on retrospective studies (n=183 patients, HR 0.77, 95% CI, 0.50 to 1.19, P=0.24). Published evidence is sparse but does not support the use of RT in induction regimens for stage IIIA (N2). Given the potential disadvantages of adding radiation preoperatively, clinicians should consider using this treatment strategy only in the context of a clinical trial to allow better assessment of its effectiveness.	4

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
64. Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol.* 2008; 9(7):636-648.	Experimental-Tx	524 patients	To assess the additional effect of preoperative chemoradiation on tumor resection, pathological response, and survival in patients with stage III NSCLC amenable to resection.	Of 524 eligible patients, 142/264 (54%) in the interventional group and 154/260 (59%) in the control group underwent surgery; 98/264 (37%) and 84/260 (32%) underwent complete resection. In patients with complete resection, the proportion of those with mediastinal downstaging (45/98 [46%] and 24/84 [29%], P=0.02) and pathological response (59/98 [60%] and 17/84 [20%], P<0.0001) favored the interventional group. However, there was no difference in PFS (primary endpoint) between treatment groups-either in eligible patients (median PFS 9.5 months, range 1.0-117.0 [95% CI, 8.3-11.2] vs 10.0 months, range 1.0-111.0 [8.9-11.5], 5-year PFS 16% [11-21] vs 14% [10-19], HR 0.99 [0.81-1.19], P=0.87), in those undergoing tumor resection, or in patients with complete resection. In both groups, 35% of patients undergoing surgery received a pneumonectomy (50/142 vs 54/154). In patients receiving a pneumonectomy, treatment-related mortality increased in the interventional group compared with the control group (7/50 [14%] vs 3/54 [6%]).	1
65. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. *J Clin Oncol.* 2005;23(25):5883-5891.	Experimental-Tx	257 patients (arm 1, n=91; arm 2, n=74; arm 3, n=92)	To determine the optimal sequencing and integration of paclitaxel/carboplatin with standard daily thoracic RT, in patients with locally advanced unresected stage III NSCLC. Survival data were compared with historical standard sequential chemoradiotherapy data from the Radiation Therapy Oncology Group.	With a median follow-up time of 39.6 months, median OS was 13.0, 12.7, and 16.3 months for arms 1, 2, and 3, respectively. During induction chemotherapy, grade 3/4 granulocytopenia occurred in 32% and 38% of patients on study arms 1 and 2, respectively. The most common locoregional grade 3/4 toxicity during and after thoracic RT was esophagitis, which was more pronounced with the administration of concurrent chemoradiotherapy on study arms 2 and 3 (19% and 28%, respectively).	1

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
66. Vokes EE, Herndon JE, 2nd, Kelley MJ, et al. 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. *J Clin Oncol.* 2007; 25(13):1698-1704.	Experimental-Tx	366 stage III patients	Initial analysis of a randomized phase III trial to determine whether the addition of induction chemotherapy prior to chemotherapy/RT would result in improved survival.	Median survival on arm 1 is 11.4 months vs 14 months on arm 2 (P=0.154) for 254/290 targeted deaths. One year survival estimates are 48% (41%-57%) and 54% (47%-62%) respectively. Results do not support the use of induction chemotherapy followed by chemotherapy/RT as evidence based standard of care for patients with unresectable stage III NSCLC. Further follow-up required.	1
67. Amini A, Lou F, Correa AM, et al. Predictors for locoregional recurrence for clinical stage III-N2 non-small cell lung cancer with nodal downstaging after induction chemotherapy and surgery. *Ann Surg Oncol.* 2013;20(6):1934-1940.	Observational-Tx	153 patients	A retrospective analysis of the treatment outcomes of patients treated at 2 major cancer centers to determine predictors for LRR for patients with clinical stage III-N2 disease who undergo nodal downstaging after induction chemotherapy at the time of surgery.	Median follow-up was 39.3 months. Pretreatment N2 status was confirmed pathologically (18.2 %) or by PET/CT (81.8%). Overall, the 5-year LRR rate was 30.8% (n = 38), with LRR being the first site of failure in 51% (22/+99877943). 5-year OS for patients with LRR compared with those without was 21% vs 60.1% (P<0.001). Using multivariate analysis, significant predictors for LRR were pN1 disease at time of surgery (P<0.001, HR 3.43, 95% CI, 1.80–6.56) and a trend for squamous histology (P=0.072, HR 1.93, 95% CI, 0.94–3.98). 5-year LRR rate for pN1 vs pN0 disease was 62% vs 20%. Neither single vs multistation N2 disease (P=0.291) nor initial staging technique (P=0.306) were predictors for LRR. N1 status also was predictive for higher distant recurrence (P=0.021, HR 1.91, 95% CI, 1.1–3.3) but only trended for poorer survival (P=0.123, HR 1.48, 95% CI, 0.9–2.44).	2

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
68. Koshy M, Goloubeva O, Suntharalingam M. Impact of neoadjuvant radiation on survival in stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2011; 79(5):1388-1394.	Observational-Tx	48,131 patients	Retrospective study to assess the impact of neoadjuvant RT for stage III NSCLC.	By type of treatment, the 3-year OS was 10% with RT, 37% with surgery, 34% with surgery and PORT, and 45% with neoadjuvant radiation followed by surgery (P=0.0001). Multivariable Cox model identified sex, race, laterality, T stage, N stage, and type of treatment as factors affecting survival. Estimated HRs adjusted for other variables in regression model showed the types of treatment: Surgery (HR, 1.3; 95% CI, 1.2-1.4), surgery-RT (HR, 1.2; 95% CI, 1.1-1.3), and RT (HR, 2.3; 95% CI, 2.15-2.53) were associated with significantly worse OS when compared with neoadjuvant-RT (P=0.0001).	2
69. Dillman RO, Herndon J, Seagren SL, Eaton WL, Jr., Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst.* 1996; 88(17):1210-1215.	Experimental-Tx	155 patients (78 in chemotherapy/RT group and 77 in RT group)	Report provides data for 7 years of follow-up of patients enrolled in the Cancer and Leukemia Group B (CALGB) trial. The CALGB trial is a randomized trial that showed that induction chemotherapy before RT improved survival during the first 3 years of follow-up.	After more than 7 years of follow-up, the median survival remains greater for the chemotherapy-RT group (13.7 months) than for the RT group (9.6 months) (P=.012). The percentages of patients surviving after years 1 through 7 were 54, 26, 24, 19, 17, 13, and 13, respectively for the chemotherapy-RT group and 40, 13, 10, 7, 6, 6, and 6, respectively for the RT group.	1
70. Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst.* 1995; 87(3):198-205.	Experimental-Tx	452 patients	Phase III trial that compares: standard RT; induction chemotherapy followed by standard RT; twice-daily RT.	Toxicity was acceptable. Compliance with protocol treatment was acceptable. One-year survival (%) and median survival (months) were as follows: standard RT 46%, 11.4 months; chemotherapy plus RT 60%, 13.8 months; and hyperfractionated RT 51%, 12.3 months. The chemotherapy plus RT arm was statistically superior to the other two treatment arms (log-rank P=.03).	1
71. Cesario A, Margaritora S, Trodella L, et al. Incidental surgical findings of a phase I trial of weekly gemcitabine and concurrent radiotherapy in patients with unresectable non-small cell lung cancer. *Lung Cancer.* 2002; 37(2):207-212.	Observational-Tx	30 patients	Report results of phase I trial of NSCLC patients treated with concurrent weekly gemcitabine and RT to achieve clinical downstaging so as to re-enter resectability. RT total dose: 50.4 Gy (1.8 Gy/day).	Clinical CR in 3.7%, PR in 59.2%. 14 became respectable. Pathologic downstaging occurred in 71.4%. Combined treatment with weekly gemcitabine and concurrent RT is feasible.	2

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
72. Granetzny A, Striehn E, Bosse U, et al. A phase II single-institution study of neoadjuvant stage IIIA/B chemotherapy and radiochemotherapy in non-small cell lung cancer. *Ann Thorac Surg.* 2003; 75(4):1107-1112.	Observational-Tx	26 patients	Retrospective analysis of a single-institution phase II study. Stage IIIA and IIIB resected after combined chemotherapy and radiochemotherapy.	R0 resection was achieved in 92%. Histologic remission was found in 76% of these patients. Median survival 11.4 and 34.7 months in patients with and without viable tumor cells in mediastinal lymph nodes; P=0.01).	2
73. Ichinose Y, Fukuyama Y, Asoh H, et al. Induction chemoradiotherapy and surgical resection for selected stage IIIB non-small-cell lung cancer. *Ann Thorac Surg.* 2003; 76(6):1810-1814; discussion 1815.	Observational-Tx	27 patients	Phase II trial to evaluate the efficacy and safety of combination chemotherapy using an oral combination of uracil and tegafur plus cisplatin and concurrent thoracic RT.	93% PR. The calculated 1-year and 3-year survival rates of all 27 patients were 73% and 56% respectively. Chemotherapy using uracil and tegafur plus cisplatin and concurrent RT as induction treatment and a surgical resection for patients with marginally resectable stage IIIB NSCLC is feasible and promising.	2
74. Junker K, Langner K, Klinke F, Bosse U, Thomas M. Grading of tumor regression in non-small cell lung cancer : morphology and prognosis. *Chest.* 2001; 120(5):1584-1591.	Observational-Tx	54 patients	Multicenter phase II trial to examine the applicability of a morphologic regression grading and its prognostic value.	Patients with tumors of regression grades IIb or III showed significantly longer survival times than those with tumors of regression grades I or IIa (median survival time, 36 vs 14 months, respectively; 3-year survival rate, 52% vs 9%, respectively; P=0.02). After neoadjuvant therapy of patients with NSCLC, the proposed tumor regression grading was of predictive value for long-term survival. Beyond the achievement of complete tumor resection, a therapy-induced tumor regression of <0% of vital tumor tissue is essential for superior long-term outcomes.	2
75. Kuten A, Anacak Y, Abdah-Bortnyak R, et al. Neoadjuvant radiotherapy concurrent with weekly paclitaxel and carboplatin and followed by surgery in locally advanced non-small-cell lung cancer. *Am J Clin Oncol.* 2003; 26(2):184-187.	Observational-Tx	37 patients	Phase II study to evaluate the efficacy and toxicity of neoadjuvant RT concurrent with weekly paclitaxel and carboplatin in locoregional advanced NSCLC.	CR 13.5%, PR 38%, stable disease 32.5% and progressive disease 6/37 16%. 20 patients underwent surgery. In 56% the tumor was totally resected. There was pathologic CR in 4 patients. Median survival is 22 months. Neoadjuvant RT concurrent with weekly paclitaxel/carboplatin is effective.	2
76. Law A, Karp DD, Dipetrillo T, Daly BT. Emergence of increased cerebral metastasis after high-dose preoperative radiotherapy with chemotherapy in patients with locally advanced nonsmall cell lung carcinoma. *Cancer.* 2001; 92(1):160-164.	Observational-Tx	42 consecutive patients	Consecutive patients with IIIA/IIIB NSCLC underwent induction chemoradiotherapy followed by surgical resection. Cisplatin (60 mg/m(2)) on days 1 and 22 and etoposide (100 mg/m(2)) on days 1, 2, and 3, and days 22, 23, and 24 together with 5940 cGy of radiation in 180 cGy fractions over 6 weeks.	74% underwent surgical resection of the primary lung tumor and mediastinal lymph nodes after chemoradiotherapy. For these, median survival was 52 months, 5 year survival 50% and local control 80%. Distant metastases other than brain reduced.	2

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
77. Machtay M, Lee JH, Stevenson JP, et al. Two commonly used neoadjuvant chemoradiotherapy regimens for locally advanced stage III non-small cell lung carcinoma: long-term results and associations with pathologic response. *J Thorac Cardiovasc Surg.* 2004; 127(1):108-113.	Observational-Tx	53 patients	Retrospective study to determine the outcomes (pathologic response, survival, local-regional control, and toxicity) in patients treated with neoadjuvant chemoradiotherapy and planned operation for stage IIIA NSCLC.	85% were deemed surgical candidates after induction therapy. 42% had a major pathologic response to stage 0, I, or II disease. The 5-year actuarial survival was 31%. Major pathologic response was associated with improved survival (48% vs 24%; P =.027).	2
78. Sawabata N, Keller SM, Matsumura A, et al. The impact of residual multi-level N2 disease after induction therapy for non-small cell lung cancer. *Lung Cancer.* 2003; 42(1):69-77.	Observational-Tx	131 patients	Retrospective review of patients with stages IIIa and IIIb NSCLC who had undergone induction chemotherapy and/or RT followed by surgery.	5-year survival was 54% for patients with pathologic single level N2 disease and 11% for patients with multiple N2 level disease (P<0.01).	2
79. Stamatis G, Djuric D, Eberhardt W, et al. Postoperative morbidity and mortality after induction chemoradiotherapy for locally advanced lung cancer: an analysis of 350 operated patients. *Eur J Cardiothorac Surg.* 2002; 22(2):292-297.	Observational-Tx	350 consecutive patients	Review charts of patients in the course of two phase II and one phase III studies to evaluate the frequency and risk of postoperative cardiopulmonary and bronchial complications in patients with locally advanced lung cancer after induction chemoradiotherapy and definitive surgery.	44% developed early or late complications; the hospital mortality rate was 4.9%. Analysis shows surgery can be feasible with acceptable mortality but increased morbidity.	2
80. Takita H, Shin KH. Radiation induced chemotherapy sensitization in trimodality therapy of stage III non small cell lung cancer. A preliminary report. *J Exp Clin Cancer Res.* 2000; 19(4):413-416.	Observational-Tx	18 patients	Initial report on radiation induced chemotherapy sensitization in trimodality therapy of stage III NSCLC. Eight IIIA and 10 IIIB patients initially given 20 Gy of RT in 10 fractions and then received two courses of Taxol combination chemotherapy.	The overall response rate was 83% (15/18) and 13/18 patients underwent surgery.	3
81. Veronesi G, Solli PG, Leo F, et al. Low morbidity of bronchoplastic procedures after chemotherapy for lung cancer. *Lung Cancer.* 2002; 36(1):91-97.	Observational-Tx	27 patients	Analysis of prospective series of lung resections to evaluate if induction chemotherapy, with or without irradiation, represents an additional risk factor for early and late morbidity and perioperative mortality in bronchoplastic procedures for lung cancers.	93% complete resection rate. Preoperative chemotherapy or combination of chemoradiation therapy is not associated with an additional risk of anastomotic complications in bronco and angioplastic procedures.	2
82. Martin J, Ginsberg RJ, Abolhoda A, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risks of right pneumonectomy. *Ann Thorac Surg.* 2001; 72(4):1149-1154.	Observational-Tx	470 patients	Retrospective review to determine the incidence of surgical morbidity and mortality after induction chemotherapy or chemoradiation for resectable NSCLC and identify factors that predict adverse postoperative events.	Total mortality was 7/297 (2.4%) and 11/97 (11.3%) for all lobectomies and pneumonectomies, respectively, but mortality was 11/46 (23.9%) for right pneumonectomy. Complications developed in 179 patients (38%). By multiple regression analysis, right pneumonectomy (P=0.02), blood loss (P=0.01), and forced expiratory volume in one second (percent predicted) (P=0.01) predicted complications. No factor emerged to explain this high right pneumonectomy mortality rate.	2

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
83. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet.* 2009; 374(9687):379-386.	Experimental-Tx	202-Group 1; 194-Group 2	Phase III randomized trial to compare concurrent chemotherapy and RT followed by resection with standard concurrent chemotherapy and definitive RT without resection in patients with stage T1-3pN2M0 NSCLC. Patients were assigned in 1:1 ratio to concurrent induction chemotherapy (two cycles of cisplatin [50 mg/m(2) on days 1, 8, 29, and 36] and etoposide [50 mg/m(2) on days 1-5 and 29-33]) plus RT (45 Gy) in multiple academic and community hospitals. If no progression, patients in group 1 had resection and those in group 2 continued RT uninterrupted up to 61 Gy.	Median OS was 23.6 months in group 1 and 22.2 months (9.4-52.7) in group 2. PFS was better in group 1 than in group 2, median 12.8 months (5.3-42.2) vs 10.5 months (4.8-20.6). Neutropenia and oesophagitis were the main grade 3 or 4 toxicities associated with chemotherapy plus RT in group 1 (77 [38%] and 20 [10%], respectively) and group 2 (80 [41%] and 44 [23%], respectively). Chemotherapy plus RT with or without resection (preferably lobectomy) are options for patients with stage IIIA (N2) NSCLC.	1
84. Daly BD, Cerfolio RJ, Krasna MJ. Role of surgery following induction therapy for stage III non-small cell lung cancer. *Surg Oncol Clin N Am.* 2011; 20(4):721-732.	Review/Other-Tx	N/A	To review role of surgery following induction therapy for stage III NSCLC.	Radiation when given as part of the induction protocol appears to offer a higher rate of resection and complete resection, and higher doses of radiation are associated with better nodal downstaging. Resection in patients with persistent N2 disease and pneumonectomy following induction therapy remain controversial. Resection in patients with persistent N2 disease and pneumonectomy following induction therapy remain controversial.	4
85. De Craene S, Surmont V, van Meerbeeck JP. Adjuvant or neoadjuvant chemotherapy in minimal N2 stage IIIA nonsmall cell lung cancer. *Curr Opin Oncol.* 2010; 22(2):102-111.	Review/Other-Tx	N/A	To review the recent data on perioperative chemotherapy in stage III A-N2 NSCLC and present future research opportunities.	Four retrospective series, two phase 2 and four phase 3 trials in the neoadjuvant setting and one retrospective series, two phase 2 trials and two phase 3 trials in the adjuvant setting are retrieved and discussed. The available evidence does not allow to change the current recommendation regarding the management of patients presenting with biopsy-proven clinical stage IIIA-N2 NSCLC: their preferred treatment is chemoradiotherapy. Surgery with neoadjuvant or adjuvant chemotherapy is not proven superior to RT. The patient occasionally presenting with unforeseen pN2 despite adequate preoperative mediastinal staging should be offered ACT and possibly PORT.	4

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
86. Daly BD, Fernando HC, Ketchedjian A, et al. Pneumonectomy after high-dose radiation and concurrent chemotherapy for nonsmall cell lung cancer. *Ann Thorac Surg.* 2006; 82(1):227-231.	Observational-Tx	30 patients	To review the feasibility of pneumonectomy after high-dose RT and concurrent chemotherapy.	There were 18 right and 12 left pneumonectomies. Death occurred in 4 patients (13.3%) but in only 1 (5.6%) after right pneumonectomy. Causes of death included aspiration, bronchopleural fistula, pneumonia, and massive pulmonary embolus. Major morbidity occurred in 5 (pneumonia in 2 and aspiration in 3). Median hospital stay was 9 days (range, 2 to 45), and intensive care unit stay was 2 days (range, 2 to 35). Median OS was 22 months with a 5-year survival of 33%. Patients surviving operation had a median survival of 33 months and a 5-year survival of 38%.	2
87. Gaissert HA, Keum DY, Wright CD, et al. POINT: Operative risk of pneumonectomy--influence of preoperative induction therapy. *J Thorac Cardiovasc Surg.* 2009; 138(2):289-294.	Observational-Tx	183 patients	To review a consecutive series of pneumonectomies to determine the impact of induction therapy on operative mortality.	Over a 15-year period, 183 patients underwent pneumonectomy for lung cancer. 46 received combined preoperative radiochemotherapy (25.2%) and 137 patients underwent resection only. Indications for induction therapy were stage IIB disease in 1, IIIA in 35, IIIB in 8, and IV in 2 patients. Patients receiving induction therapy were younger (mean age 58.4 vs 61.9 years; P=.033), had less heart disease (6.5% vs 26.3%; P=.0035), higher preoperative forced expiratory volume in 1 second (2.48 vs 2.13 L; P=.0018), a lower rate of endobronchial tumor (34.8% vs 67.2%; P=.0002), and underwent intrapericardial procedures more often (71.7% vs 43.1%; P=.0011). Hospital mortality was 4.3 % (2/46) after preoperative therapy and 6.6% (9/137) after resection only (P=.73); the difference in cardiopulmonary morbidity was not significant (51.1% vs 40.4%; P=.22). Induction did not predict hospital mortality after adjustment for a propensity score derived from nonoperative and operative variables correlated with neoadjuvant therapy.	2

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
88. Caglar HB, Baldini EH, Othus M, et al. Outcomes of patients with stage III nonsmall cell lung cancer treated with chemotherapy and radiation with and without surgery. *Cancer.* 2009; 115(18):4156-4166.	Observational-Tx	144 patients	To identify the factors associated with improved outcome after treatment for stage III NSCLC.	The median follow-up was 15 months (range, 3-64 months), the median potential follow-up was 37 months (range, 12-84 months), and the median OS was 22 months (95% CI, 15-28 months). The 1-year and 2-year survival rates were 68% and 47%, respectively. Among the 44 patients who underwent resection, the median survival was 61 months, and the 2-year survival rate was 73%. On multivariate analysis, stage at the time of treatment (stage IIIA vs stage IIIB) and use of surgery were the only factors associated with improved outcome (P=.01 and P=.001, respectively).	2
89. Deutsch M, Crawford J, Leopold K, et al. Phase II study of neoadjuvant chemotherapy and radiation therapy with thoracotomy in the treatment of clinically staged IIIA non-small cell lung cancer. *Cancer.* 1994; 74(4):1243-1252.	Observational-Tx	28 patients	To assess the ability of administering to patients induction chemotherapy with carboplatin and etoposide, followed by full-course RT and weekly carboplatin with tolerable toxicity as preoperative therapy to down-stage disease thus allowing the resection of clinically staged IIIA NSCLC.	52 cycles of induction chemotherapy were administered. The average initial dose of carboplatin was 407 mg/m2. Toxicity was tolerable with grade 3-4 neutropenia and/or thrombocytopenia in 48% and 27% of the patients. There were no septic deaths. Full-dose RT was administered to 82% of patients, with 73% receiving at least five weekly doses of carboplatin. The radiographically assessed response rate to the neoadjuvant treatment was 64% (PR, 46%; minimal response, 18%). 16 patients underwent gross tumor resection with 12 (43%) having negative pathologic margins. 6 patients had pneumonectomy. There were three perioperative deaths (19%); two were secondary to respiratory failure after the patients underwent a pneumonectomy. The median survival for all 28 patients was 15 months, and for the 16 patients undergoing thoracotomy was 23 months. 8 patients were alive and in remission, with follow-up ranging from 8 to 31 months.	2

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
90. Fowler WC, Langer CJ, Curran WJ, Jr., Keller SM. Postoperative complications after combined neoadjuvant treatment of lung cancer. *Ann Thorac Surg.* 1993; 55(4):986-989.	Observational-Tx	13 patients	To assess the postoperative morbidity and mortality associated with aggressive neoadjuvant therapy, the authors reviewed the records of patients who underwent resection of locally advanced NSCLC after 2 monthly cycles of infusional 5-fluorouracil, 640 to 800 mg/m2 (days 1 through 5); cisplatin, 20 mg/m2 (days 1 through 5); etoposide, 50 mg/m2 (days 1, 3, and 5); and concomitant radical thoracic irradiation (6,000 cGy) administered in 200-cGy daily fractions.	6 patients underwent lobectomy with no mortality, whereas 7 pneumonectomies were associated with 3 deaths (43%). Culture-negative, diffuse pulmonary infiltrates developed 3 to 6 days after operation in 5/7 pneumonectomy patients and in 1/6 lobectomy patients. 2 patients who had undergone pneumonectomy died of progressive adult respiratory distress syndrome. A third death resulted from a bronchopleural fistula that developed 30 days after pneumonectomy. Morbidity and mortality were not associated with preoperative pulmonary function test results, nutritional status, or intraoperative inspired oxygen fraction (P>0.05 by chi 2 test). Only pneumonectomy correlated with increased morbidity and mortality (P<0.05 by chi 2 test).	2

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
91. Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. *Ann Thorac Surg*. 2004; 78(4):1200-1205; discussion 1206.	Observational-Tx	40 patients	To report a series of patients with locally advanced NSCLC who successfully underwent pulmonary resection after receiving greater than 59 Gy radiation and concurrent chemotherapy. Operative results and midterm survival follow-up are presented.	Preoperative stage was IIb (7 patients), IIIA (21 patients), IIIB (10 patients), and IV (2 patients with isolated brain metastasis). 13 patients exhibited Pancoast tumors. Median time from completion of induction therapy to surgery was 53 days. 29 lobectomies and 11 pneumonectomies (7 right, 4 left) were performed. There were no postoperative deaths. Intercostal muscle flaps were used prophylactically in all but one pneumonectomy patient. 7 patients required perioperative transfusions. Median intensive care unit time averaged 2 days and the total length of stay was 6 days. One patient exhibited postpneumonectomy pulmonary edema and a bronchopleural fistula developed in another patient (not receiving an intercostal muscle flap). 34/40 patients (85%; 95% CI: 70%-94%) were downstaged pathologically, 33/40 patients (82.5%, 95% CI [CI]: 67%-93%) indicated no residual lymphadenopathy, and 18/40 patients (45%, 95% CI: 29%-61%) exhibited a complete pathologic response. Median follow-up was 2.8 years. The 1-, 2-, and 5-year OS rates were 92.4%, 66.7%, and 46.2%, respectively. Disease-free 1-, 2-, and 5-year survival rates were 73.0%, 67.2%, and 56.4%, respectively. Median DFS has not been reached.	3

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
92. Vora SA, Daly BD, Blaszkowsky L, et al. High dose radiation therapy and chemotherapy as induction treatment for stage III nonsmall cell lung carcinoma. *Cancer.* 2000; 89(9):1946-1952.	Observational-Tx	42 patients	To review the authors' experience in treating consecutive patients with American Joint Committee on Cancer (1997 revision) Stage III NSCLC with aggressive preoperative chemoradiation followed by surgical resection.	42 patients received preoperative chemoradiation, 33 of whom underwent surgical resection (79%), including 9 patients who underwent pneumonectomies. Complete pathologic responses were observed in 27% of these patients. Postoperative complications were noted in 21% of the patients and included persistent air leak, supraventricular arrhythmia, and empyema. There were no reported treatment-related deaths. The median follow-up was 26 months. The overall 5-year survival rate for all patients was 36.5% and was 45.3% for patients who underwent resection. A trend toward increased 5-year survival was observed in patients who had a complete pathologic response (57.1%). Univariate analysis revealed the N stage classification to be significant for predicting a CR. Patterns of failure revealed the brain to be the most common site of first recurrence (50%) and the only site of recurrence in 36% of patients. There was only one case of local failure.	2
93. Suntharalingam M, Paulus R, Edelman MJ, et al. Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys.* 2012; 84(2):456-463.	Observational-Tx	57 patients	To evaluate mediastinal nodal clearance rates after induction chemotherapy and concurrent, full-dose RT in a phase II trimodality trial (Radiation Therapy Oncology Group protocol 0229).	The grade 3/4 toxicities included hematologic 35%, gastrointestinal 14%, and pulmonary 23%. 43 patients (75%) were evaluable for the primary endpoint. 27 patients achieved the primary endpoint of mediastinal nodal clearance (63%). 37 patients underwent resection. There was a 14% incidence of grade 3 postoperative pulmonary complications and 1 30-day, postoperative grade 5 toxicity (3%). With a median follow-up of 24 months for all patients, the 2-year OS rate was 54%, and the 2-year PFS rate was 33%. The 2-year OS rate was 75% for those who achieved nodal clearance, 52% for those with residual nodal disease, and 23% for those who were not evaluable for the primary endpoint (P=.0002).	1

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
94. Abramson Cancer Center of the University of Pennsylvania. Proton Beam Radiation Therapy and Chemotherapy in Treating Patients With Stage III Non-Small Cell Lung Cancer That Can Be Removed By Surgery. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2013 April 3. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01076231?term=NCT01076231&rank=1. NLM Identifier: NCT01076231.	Review/Other-Tx	Ongoing	To study the side effects and best dose of proton beam RT when given together with cisplatin and etoposide and to see how well it works in treating patients with stage III NSCLC that can be removed by surgery.	This trial is still recruiting study subjects and results are not available yet.	4
95. Massachusetts General Hospital. Proton Radiation Therapy With Cisplatin and Etoposide Followed by Surgery in Stage III Non-Small Cell Lung Cancer. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2013 April 3. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01565772?term=NCT01565772&rank=1. NLM Identifier: NCT01565772.	Review/Other-Tx	Ongoing	To determine the safest dose of proton RT to give in combination with standard chemotherapy in participants with NSCLC.	This trial is still recruiting study subjects and results are not available yet.	4
96. Mak RH, Doran E, Muzikansky A, et al. Outcomes after combined modality therapy for EGFR-mutant and wild-type locally advanced NSCLC. *Oncologist.* 2011; 16(6):886-895.	Observational-Tx	123 patients	To examine outcomes after combined modality therapy including thoracic RT in 123 patients with locally advanced NSCLC and known EGFR mutation status. Outcomes were compared using Kaplan-Meier analysis, the log-rank test, and multivariate Cox regression models.	All 123 patients underwent thoracic RT; 25% had tumors with EGFR mutations and 94% had stage III disease. Overall, 81% received chemotherapy concurrent with RT and 55% underwent surgical resection. With a median follow-up of 27.5 months, the OS rate was significantly higher in patients with EGFR-mutant tumors than in those with wild-type EGFR tumors (2-year estimate: 92.6% vs 69.0%; P=.04). The 2-year relapse-free survival and distant recurrence rates did not differ significantly by genotype. The 2-year LRR rate was significantly lower in EGFR-mutant than in wild-type EGFR patients (17.8% vs 41.7%; P=.005). EGFR-mutant genotype was associated with a lower risk for LRR rate on multivariate analysis, but not OS, after adjusting for surgery and other potential confounders.	2

Induction and Adjuvant Therapy for N2 NSCLC
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
97. Neal JW, Pennell NA, Govindan R, et al. The SELECT study: A multicenter phase II trial of adjuvant erlotinib in resected epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC). *ASCO Meeting Abstracts.* 2012; 30(15_suppl):7010.	Observational-Tx	36 patients	To investigate the safety and efficacy of adjuvant erlotinib in EGFR mutation-positive NSCLC.	Toxicities were typical of erlotinib; no grade 4 or 5 events or pneumonitis occurred. 8 patients (22%) required one dose reduction to 100 mg/day and 5 (14%) two reductions to 50 mg/day for grade 3 or persistent grade 2 toxicities. 11 patients discontinued before 2 full years (<1 month (month) [4], 1-12 months [2] and 12-23 months [5]) for toxicities [6], patient preference [3], prostate cancer [1] and recurrence [1]. After a median follow-up of 2.5 years, the 2 year DFS from enrollment is 94% (95% CI, 80%, 99%). 10 patients have recurred, 1 during erlotinib treatment and the others after stopping erlotinib (interval before recurrence 2 months [1], 6-12 months [4], >12 months [4]). Genotyping on repeat biopsies from 7 of the recurrent cases is underway, as is assessment of response to subsequent erlotinib therapy. 2 patients have died of recurrence: one at 1.5 years who stopped erlotinib after 1 month for toxicity, and one at 2 years who progressed while on erlotinib.	2
98. Goss GD, Lorimer I, Tsao MS, et al. A phase III randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor inhibitor gefitinb in completely resected stage IB-IIIA non-small cell lung cancer (NSCLC): NCIC CTG BR.19. *ASCO Meeting Abstracts.* 2010; 28(18_suppl):LBA7005.	Experimental-Tx	503 patients	The authors report a trial of adjuvant gefitinib vs placebo after complete resection of NSCLC. Patients were randomized to gefitinib 250 mg or placebo daily x 2 years.	Median follow-up is 4.7 years; median treatment time is 4.8 mos. For gefitinib vs placebo, median DFS is 4.2 years vs not yet reached HR1.22 (95% CI, 0.93-1.61), P=0.15 and median OS 5.1 years vs not yet reached HR 1.24 (95% CI, 0.94-1.64), P=0.14. In multivariate analysis, tumor size >4 cm was predictive of poor DFS (P<0.0001) and never smoking for better OS with gefitinib (P=0.02). Results for KRAS and EGFR copy are available on 350 and 348 patients respectively. KRAS mutations were neither prognostic HR 1.12 (95% CI, 0.67-1.86), P=0.66 nor predictive of gefitinib benefit (P=0.16) on OS. EGFR copy whether low/high polysomy or amplification was neither prognostic (P=0.77) nor predictive of OS benefit from gefitinib.	1

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

ACT = Adjuvant cisplatin-based chemotherapy

CI = Confidence interval

CR = Complete response

CT = Computed tomography

DFS = Disease-free survival

HR = Hazard ratio

LRR = Locoregional recurrence

MRI = Magnetic resonance imaging

NSCLC = Non-small-cell lung cancer

OS = Overall survival

PET = Positron emission tomography

PFS = Progression-free survival

PORT = Postoperative radiotherapy

PR = Partial response

RR = Relative risk

RT = Radiation therapy

SBRT = Stereotactic body radiation therapy

TNM = Tumor, node, metastasis

US = Ultrasound