Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Curran WJ, Jr., Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst.* 2011;103(19):1452-1460.	Experimental-Tx	610 patients	To compare concurrent once-daily radiation with sequential therapy and then the better of those two against concurrent twice-daily radiation to determine whether the rate of OS is improved by concurrent and/or hyperfractionated RT administration.	Median survival times were 14.6, 17.0, and 15.6 months for arms 1–3, respectively. 5-year survival was statistically significantly higher for patients treated with the concurrent regimen with once-daily TRT compared with the sequential treatment (5-year survival: sequential, arm 1, 10% [20 patients], 95% CI, 7%–15%; concurrent, arm 2, 16% [31 patients], 95% CI, 11%–22%, P=.046; concurrent, arm 3, 13% [22 patients], 95% CI, 9%–18%). With a median follow-up time of 11 years, the rates of acute grade 3–5 nonhematologic toxic effects were higher with concurrent than sequential therapy, but late toxic effects were similar.	1
2. Bradley JD, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617. *ASCO Meeting Abstracts.* 2013;31(15_suppl):7501.	Experimental-Tx	464 patients	To compare the OS of patients treated with standard-dose (60Gy) vs high-dose (74Gy) RT with concurrent chemotherapy.	464 patients were accrued prior to closure of the high-dose arm in 6/11, of which 419 were eligible for analysis. Median follow up was 17.2 months. There were 2 and 10 grade 5 treatment-related adverse events on the standard-dose and high-dose arms, respectively. Grade 3+ adverse events were 74.2% and 78.2% on standard-dose and high-dose arms, respectively (P=0.34).The median survival times and 18-month OS rates for the standard-dose and high-dose arms were 28.7 vs 19.5 months, and 66.9% vs 53.9% respectively (P=0.0007). The primary cause of death was lung cancer (72.2% vs 73.5%) (P=0.84). Local failure rates at 18 months were 25.1% vs 34.3% for standard-dose and high-dose patients, respectively (P=0.03). Local-regional and distant failures at 18 months were 35.3% vs 44% (P=0.04) and 42.4% vs 47.8% (P=0.16) for standard-dose and high-dose arms, respectively. Factors predictive of less favorable OS on multivariate analysis were higher radiation dose, higher esophagitis/dysphagia grade, greater gross tumor volume, and heart volume >5 Gy.	1

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
3. Chang JY, Cox JD. Improving radiation conformality in the treatment of non-small cell lung cancer. *Semin Radiat Oncol.* 2010;20(3):171-177.	Review/Other-Tx	N/A	Review conformal RT in the treatment of NSCLC.	No results stated in abstract.	4
4. Ausborn NL, Le QT, Bradley JD, et al. Molecular profiling to optimize treatment in non-small cell lung cancer: a review of potential molecular targets for radiation therapy by the translational research program of the radiation therapy oncology group. *Int J Radiat Oncol Biol Phys.* 2012;83(4):e453-464.	Review/Other-Tx	N/A	To review molecular pathways that can be targeted in conjunction with RT in patients with advanced NSCLC and strategies for their selection.	No results stated in abstract.	4
5. 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 Monte Carlo method and to provide the framework upon which to build a comprehensive program for commissioning and routine quality assurance of Monte Carlo-based treatment planning systems.	No results stated in abstract.	4
6. 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
7. 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 April 24, 2014.	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.	This trial is still recruiting study subjects and results are not available yet.	4

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
8. 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 April 24, 2014.	Review/Other-Tx	Ongoing	To compare the overall survival of patients treated with high-dose vs standard-dose conformal radiation therapy in the setting of concurrent chemotherapy; To compare the overall survival of patients treated with cetuximab vs without cetuximab in the setting of concurrent chemotherapy.	This trial is still recruiting study subjects and results are not available yet.	4
9. 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 April 24, 2014.	Review/Other-Tx	Ongoing	To determine the rate of 1-year grade 3 or higher adverse events definitely, probably, or possibly related to treatment.	This trial is still recruiting study subjects and results are not available yet.	4
10. 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
11. Perez CA, Stanley K, Rubin P, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Preliminary report by the Radiation Therapy Oncology Group. *Cancer.* 1980;45(11):2744-2753.	Experimental-Tx	365 patients	Preliminary analysis of a prospective randomized study involving patients with histologically proven unresectable non-oat-cell carcinoma of the lung treated with definitive RT.	For patients who achieved complete regression of the tumor following irradiation, the 2-year survival rate is 40%, in contrast to 20% for those with partial regression, and no survivors among the patients with stable or progressive disease. The incidence of intrathoracic recurrence was 33% for patients treated with 6000 rad, 39% for those receiving 5000 rad, and 44%–49% for those treated with a 4000-rad split or continuous course. At present, the data strongly suggest that patients treated with 5000 or 6000 rad have a better response, tumor control, and survival rate than those receiving lower doses. However, additional follow-up of patients at risk in each group will be necessary before a final conclusion is drawn.	1

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
12. Rosenzweig KE, Sim SE, Mychalczak B, Braban LE, Schindelheim R, Leibel SA. Elective nodal irradiation in the treatment of non-small-cell lung cancer with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys.* 2001;50(3):681-685.	Observational-Tx	171 patients	To measure the rate of regional failure without elective RT to uninvolved lymph nodes.	Only 11 patients (6.4%) with elective nodal failure were identified. With a median follow-up of 21 months in survivors, the 2-year actuarial rates of elective nodal control and primary tumor control were 91% and 38%, respectively. In patients who were locally controlled, the 2-year rate of elective nodal control was 85%. The median time to elective nodal failure was 4 months (range, 1-19 months). Most patients failed in multiple lymph node regions simultaneously.	3
13. Senan S, Burgers S, Samson MJ, et al. Can elective nodal irradiation be omitted in stage III non-small-cell lung cancer? Analysis of recurrences in a phase II study of induction chemotherapy and involved-field radiotherapy. *Int J Radiat Oncol Biol Phys.* 2002;54(4):999-1006.	Observational-Tx	50 patients	To establish the recurrence patterns when elective mediastinal irradiation was omitted, patients with stage III NSCLC were treated with sequential chemotherapy and IFRT.	Of 43 patients who received doses ≥50 Gy, 35% were disease free at last follow-up; in-field recurrences developed in 27% (of whom 16% had exclusively in-field recurrences); 18% had distant metastases exclusively. No elective nodal failure was observed. The median actuarial OS was 18 months (95% CI, 14-22) and the median PFS was 12 months (95% CI, 6-18).	1
14. Sulman EP, Komaki R, Klopp AH, Cox JD, Chang JY. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. *Radiat Oncol.* 2009;4:5.	Observational-Tx	115 patients	To determine the frequency of elective nodal failure and in-field failure, the authors examined a large cohort of patients with NSCLC staged with PET/CT and treated with 3D-CRT that excluded uninvolved lymph node stations.	The median follow-up time was 18 months (3 to 44 months) among all patients and 27 months (6 to 44 months) among survivors. The median OS, 2-year actuarial OS and disease-free survival were 19 months, 38%, and 28%, respectively. The majority of patients died from distant metastases, the overall rate of which was 36%. Of the 31 patients with local regional failure, 26 (22.6%) had in-field failure, 5 (4.3%) had elective nodal failure and 2 (1.7%) had isolated elective nodal failure. For 88 patients with stage IIIA/B, the frequencies of in-field failure, any elective nodal failure, isolated elective nodal failure, and distant metastases were 23 (26%), 3 (9%), 1 (1.1%) and 36 (40.9%), respectively. The comparable rates for the 22 patients with early stage node-negative disease (stage IA/IB) were 3 (13.6%), 1(4.5%), 0 (0%), and 5 (22.7%), respectively.	2

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
15. Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *Am J Clin Oncol.* 2007;30(3):239-244.	Experimental-Tx	200 patients	A randomized study of IFRT vs elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III NSCLC.	Patients in the IFRT arm achieved better overall response rate (90% vs 79%, P=0.032) and better 5-years local control rate (51% vs 36%, P=0.032) than those in the elective nodal irradiation arm. The radiation pneumonitis rate in patients with IFRT was lower than in patients with elective nodal irradiation (17% vs 29%, P=0.044), and similar trends appeared in the radiation esophagitis, myelosuppression, and radiation pericarditis between 2 study arms, although not significantly. The 1-, 2-, and 5-year survival rates were 60.4%, 25.6%, and 18.3% for the elective nodal irradiation arm and 69.9%, 39.4%, and 25.1% for the IFRT arm, respectively. Only the 2-year survival rates were statistically significant (P=0.048).	1
16. Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF. A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. *J Clin Oncol.* 1990;8(9):1543-1555.	Experimental-Tx	848 patients	A randomized phase I/II trial of hyperfractionated RT with total doses of 60.0 Gy to 79.2 Gy to examine the possible survival benefit with ≥69.6 Gy in favorable patients with Radiation Therapy Oncology Group (RTOG) stage III NSCLC.	No significant differences in the risks of acute or late effects in normal tissues were found among the 848 patients analyzed in the 5 arms; risks of severe or life-threatening pneumonitis were 2.6% for 60.0 to 64.8 Gy, 5.7% for 69.6 to 74.4 Gy, and 8.1% for 79.2 Gy. Among 350 patients who had the same criteria as Cancer and Leukemia Group B (CALGB) protocol 84-33 (American Joint Committee on Cancer Staging [AJCCS], 1984, stage III; Karnofsky performance status 70 to 100; less than 6% weight loss), there was a dose response for survival: survival with 69.6 Gy (median, 13.0 months; 2 years, 29%) was significantly (P=.02) better than the lower total doses. There were no differences in survival among the 3 highest total-dose arms. Comparisons with results in similar patients treated with 60 Gy in 30 fractions of 2.0 Gy 5 days per week for 6 weeks suggest benefit from hyperfractionated RT with 69.6 Gy.	1

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

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17. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiother Oncol.* 1999;52(2):137-148.	Experimental-Tx	563 patients	To compare continuous, hyperfractionated, accelerated RT which employs 36 fractions of 1.5 Gy 3 times per day to give 54 Gy in 12 consecutive days with conventional RT 30 fractions of 2 Gy to a total dose of 60 Gy in 6 weeks in a randomized controlled trial in locally advanced NSCLC.	Overall there was a 22% reduction in the RR of death, which is equivalent to an absolute improvement in 2 year survival of 9% from 20% to 29% (P=0.008) and a 21% reduction in the RR of local progression (P=0.033). In the large subgroup of patients with squamous cell cancer which accounted for 81% of the cases, there was a 30% reduction in the RR of death, which is equivalent to an absolute improvement in 2 year survival of 13% from 20% to 33% (P=0.0007) and a 27% reduction in the RR of local progression (P=0.012). Furthermore, in squamous carcinoma there was a 25% reduction in the RR of local and/or distant progression (P=0.025) and 24% reduction in the RR of metastasis (P=0.043). There was no evidence that continuous, hyperfractionated, accelerated RT gave more or less benefit in any other subgroup.	1
18. Baumann M, Herrmann T, Koch R, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). *Radiother Oncol.* 2011;100(1):76-85.	Experimental-Tx	406 patients	A phase III randomized trial that compares 3D-conformal external beam radiotherapy using the CHARTWEL protocol to a total dose of 60 Gy within 2.5 weeks conventionally fractionated to 66 Gy within 6.5 weeks.	OS, primary endpoint at 2-, 3- and 5-years was not significantly different after CHARTWEL (31%, 22% and 11%) versus conventionally fractionated (32%, 18% and 7%; HR 0.92, 95% CI, 0.75–1.13, P=0.43). Also local tumor control rates and distant metastases did not significantly differ. Acute dysphagia and radiological pneumonitis were more pronounced after CHARTWEL, without differences in clinical signs of pneumopathy. Exploratory analysis revealed a significant trend for improved local control after CHARTWEL versus conventionally fractionated with increasing UICC, T or N stage (P=0.006–0.025) and after neoadjuvant chemotherapy (HR 0.48, 0.26-0.89, P=0.019).	1

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

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19. Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys.* 2005;63(2):324-333.	Observational-Tx	106 patients	To determine whether high-dose radiation leads to improved outcomes in patients with NSCLC.	Median survival was 19 months, and 5-year OS was 13%. Multivariate analysis revealed weight loss (P=0.011) and radiation dose (P=0.0006) were significant predictors for OS. The 5-year OS was 4%, 22%, and 28% for patients receiving 63-69, 74-84, and 92-103 Gy, respectively. Although presence of nodal disease was negatively associated with locoregional control under univariate analysis, radiation dose was the only significant predictor when multiple variables were included (P=0.015). The 5-year control rate was 12%, 35%, and 49% for 63-69, 74-84, and 92-103 Gy, respectively.	2
20. Machtay M, Paulus R, Moughan J, et al. Defining local-regional control and its importance in locally advanced non-small cell lung carcinoma. *J Thorac Oncol.* 2012;7(4):716-722.	Review/Other-Tx	1,390 patients	Several analyses of the RTOG database was performed to examine the probability of local-regional control after chemoradiotherapy. The study specifically evaluates 2 different definitions of local-regional control: 1) The "traditional" RTOG measure of local-regional control, also referred to as Freedom from Local Progression; and 2) A more rigorous definition of local-regional control which requires objective local-regional tumor response in addition to freedom from local progression, similar to the definition of local-regional control often used in studies of head and neck cancer.	The local-regional control rate at 3 years was 38% based on the freedom from local progression-local-regional control definition and 14% based on the strict-local-regional control definition. Performance status, concurrent chemotherapy and RT dose intensity were associated with better local-regional control (using either definition). With the strict-local-regional control definition (but not freedom from local progression-local-regional control), age was also important. There was a powerful association between local-regional control and OS (P<0.0001) on univariate and multivariate analyses. Age, performance status, chemotherapy sequencing and RT dose intensity were also significantly associated with survival. Histology and gender were also significant if the strict-local-regional control model was used.	4

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

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21. Chang JY, Liu H, Balter P, et al. Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. *Radiat Oncol*. 2012;7:152.	Observational-Tx	130 patients	To identify predictors of survival and pneumonitis after stereotactic ablative RT for NSCLC in a relatively large single-institution series.	At a median follow-up time of 26 months, the 2-year local control rate was 98.5%. The median OS time was 60 months, and OS rates were 93.0% at 1 year, 78.2% at 2 years, and 65.3% at 3 years. No patient experienced grade 4-5 toxicity; 15 had radiation pneumonitis (12 [9.3%] grade 2 and 3 [2.3%] grade 3). Performance status, standardized uptake value max on staging PET/CT, tumor histology, and disease operability were associated with OS on univariate analysis, but only staging standardized uptake value max was independently predictive on multivariate analysis (P=0.034). Dosimetric factors were associated with radiation pneumonitis on univariate analysis, but only mean ipsilateral lung dose ≥9.14 Gy was significant on multivariate analysis (P=0.005).	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
22. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. 2010;303(11):1070-1076.	Observational-Tx	55 patients	To evaluate the toxicity and efficacy of stereotactic body RT in a high-risk population of patients with early stage but medically inoperable lung cancer.	A total of 59 patients accrued, of which 55 were evaluable (44 patients with T1 tumors and 11 patients with T2 tumors) with a median follow-up of 34.4 months (range, 4.8-49.9 months). Only 1 patient had a primary tumor failure; the estimated 3-year primary tumor control rate was 97.6% (95% CI, 84.3%-99.7%). Three patients had recurrence within the involved lobe; the 3-year primary tumor and involved lobe (local) control rate was 90.6% (95% CI, 76.0%-96.5%). Two patients experienced regional failure; the local-regional control rate was 87.2% (95% CI, 71.0%-94.7%). 11 patients experienced disseminated recurrence; the 3-year rate of disseminated failure was 22.1% (95% CI, 12.3%-37.8%). The rates for disease-free survival and OS at 3 years were 48.3% (95% CI, 34.4%-60.8%) and 55.8% (95% CI, 41.6%-67.9%), respectively. The median OS was 48.1 months (95% CI, 29.6 months to not reached). Protocol-specified treatment-related grade 3 adverse events were reported in 7 patients (12.7%; 95% CI, 9.6%-15.8%); grade 4 adverse events were reported in 2 patients (3.6%; 95% CI, 2.7%-4.5%). No grade 5 adverse events were reported.	2
23. Gomez DR, Gillin M, Liao Z, et al. Phase 1 study of dose escalation in hypofractionated proton beam therapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2013;86(4):665-670.	Review/Other-Tx	25 patients	Prospective phase I study to assess the safety of dose-escalating hypofractionated proton therapy, given without chemotherapy, for NSCLC.	The median follow-up time for patients alive at the time of analysis was 13 months (range, 8-28 months). 15 patients received treatment to hilar or mediastinal lymph nodes. Two patients experienced dose-limiting toxicity possibly related to treatment; 1 received 3.5-Gy(relative biological effectiveness) fractions and experienced an in-field tracheoesophageal fistula 9 months after proton beam therapy and 1 month after bevacizumab. The other patient received 4-Gy(relative biological effectiveness) fractions and was hospitalized for bacterial pneumonia/radiation pneumonitis 4 months after proton beam therapy.	4

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

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24. Murshed H, Liu HH, Liao Z, et al. Dose and volume reduction for normal lung using intensity-modulated radiotherapy for advanced-stage non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2004;58(4):1258-1267.	Observational-Tx	41 patients	To investigate dosimetric improvements with respect to tumor-dose conformity and normal tissue sparing using IMRT compared with 3D-CRT for advanced-stage NSCLC.	Using IMRT, the median absolute reduction in the percentage of lung volume irradiated to >10 and >20 Gy was 7% and 10%, respectively. This corresponded to a decrease of >2 Gy in the total lung mean dose and of 10% in the risk of radiation pneumonitis. The volumes of the heart and esophagus irradiated to >40-50 Gy and normal thoracic tissue volume irradiated to >10-40 Gy were reduced using the IMRT plans. A marginal increase occurred in the spinal cord maximal dose and lung volume >5 Gy in the IMRT plans, which could be have resulted from the significant increase in monitor units and thus leakage dose in IMRT.	3
25. Yom SS, Liao Z, Liu HH, et al. Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2007;68(1):94-102.	Observational-Tx	151 patients	To investigate the rate of high-grade treatment-related pneumonitis in patients with advanced NSCLC treated with concurrent chemotherapy and IMRT.	The median follow-up durations for the IMRT and 3D-CRT patients were 8 months (range, 0-27 months) and 9 months (range, 0-56 months), respectively. The median IMRT and 3D-CRT doses were 63 Gy. The median gross tumor volume was 194 mL (range, 21-911 mL) for IMRT, compared with 142 mL (range, 1.5-1,186 mL) for 3D-CRT (P=0.002). Despite the IMRT group's larger gross tumor volume, the rate of Grade ≥3 treatment-related pneumonitis at 12 months was 8% (95% CI, 4%-19%), compared with 32% (95% CI, 26%-40%) for 3D-CRT (P=0.002).	2
26. Liao ZX, Komaki RR, Thames HD, Jr., et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2010;76(3):775-781.	Observational-Tx	496 patients	To compare disease outcomes and toxicity in patients treated with concomitant chemotherapy and either 4-D CT/IMRT or 3D-CRT.	Mean follow-up times in the 4-D CT/IMRT and CT/3D-CRT groups were 1.3 (range, 0.1-3.2) and 2.1 (range, 0.1-7.9) years, respectively. The HRs for 4-D CT/IMRT were <1 for all disease end points; the difference was significant only for OS. The toxicity rate was significantly lower in the IMRT/4-D CT group than in the CT/3D-CRT group. V20 was significantly higher in the 3D-CRT group and was a significant factor in determining toxicity. Freedom from distant metastases was nearly identical in both groups.	2

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27. Sura S, Gupta V, Yorke E, Jackson A, Amols H, Rosenzweig KE. Intensity-modulated radiation therapy (IMRT) for inoperable non-small cell lung cancer: the Memorial Sloan-Kettering Cancer Center (MSKCC) experience. *Radiother Oncol.* 2008;87(1):17-23.	Observational-Tx	55 patients	The authors review their experience with IMRT for patients with inoperable NSCLC.	With a median follow-up of 26 months, the 2-year local control and OS rates for stage I/II patients were 50% and 55%, respectively. For the stage III patients, 2-year local control and OS rates were 58% and 58%, respectively, with a median survival time of 25 months. Six patients (11%) experienced grade 3 acute pulmonary toxicity. There were no acute treatment-related deaths. Two patients (4%) had grade 3 or worse late treatment-related pulmonary toxicity.	2
28. Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2006;65(4):1087-1096.	Observational-Tx	25 patients	To compare dose-volume histograms in patients with NSCLC treated by photon or proton RT.	For stage I, the mean total lung V5, V10, and V20 were 31.8%, 24.6%, and 15.8%, respectively, for photon 3D-CRT with 66 Gy, whereas they were 13.4%, 12.3%, and 10.9%, respectively, with proton with dose escalation to 87.5 cobalt Gray equivalents (P=0.002). For stage III, the mean total lung V5, V10, and V20 were 54.1%, 46.9%, and 34.8%, respectively, for photon 3D-CRT with 63 Gy, whereas they were 39.7%, 36.6%, and 31.6%, respectively, for proton with dose escalation to 74 cobalt Gray equivalents (P=0.002). In all cases, the doses to lung, spinal cord, heart, esophagus, and integral dose were lower with proton therapy even compared with IMRT.	2
29. Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer.* 2011;117(20):4707-4713.	Observational-Tx	44 patients	To improve the toxicity of conventional concurrent chemoradiation therapy for stage III NSCLC by using proton-beam therapy to escalate the radiation dose to the tumor. The authors reported early results of a phase 2 study of high-dose proton therapy and concurrent chemotherapy in terms of toxicity, failure patterns, and survival.	Median follow-up time was 19.7 months (range, 6.1-44.4 months), and median OS time was 29.4 months. No patient experienced grade 4 or 5 proton-related adverse events. The most common nonhematologic grade 3 toxicities were dermatitis (n = 5), esophagitis (n = 5), and pneumonitis (n = 1). Nine (20.5%) patients experienced local disease recurrence, but only 4 (9.1%) had isolated local failure. Four (9.1%) patients had regional lymph node recurrence, but only 1 (2.3%) had isolated regional recurrence. 19 (43.2%) patients developed distant metastasis. The OS and PFS rates were 86% and 63% at 1 year.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. M.D. Anderson Cancer Center. Image-Guided Adaptive Conformal Photon Versus Proton Therapy. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). July 29, 2013. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00915005?term=NCT00915005&rank=1. NLM Identifier: NCT00915005.	Review/Other-Tx	Ongoing	To learn if, compared with regular x-ray radiation, proton radiation reduces the risk of developing, treatment-related pneumonitis or tumor recurrence (the tumor coming back in the irradiated area after treatment) in patients with lung cancer.	This trial is still recruiting study subjects and results are not yet available.	4
31. Koay EJ, Lege D, Mohan R, Komaki R, Cox JD, Chang JY. Adaptive/nonadaptive proton radiation planning and outcomes in a phase II trial for locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2012;84(5):1093-1100.	Observational-Tx	44 patients	To analyze dosimetric variables and outcomes after adaptive replanning of RT during concurrent high-dose protons and chemotherapy for locally advanced NSCLC.	At a median follow-up of 21.2 months (median OS, 29.6 months), no differences were found in local, regional, or distant failure or OS between groups. Adaptive planning was used more often for large tumors that shrank to a greater extent (median, 107.1 cm(3) adaptive and 86.4 cm(3) nonadaptive; median changes in volume, 25.3% adaptive and 1.2% nonadaptive; P<.01). The median number of fractions delivered using adaptive planning was 13 (range, 4-22). Adaptive planning generally improved sparing of the esophagus (median absolute decrease in V(70), 1.8%; range, 0%-22.9%) and spinal cord (median absolute change in maximum dose, 3.7 Gy; range, 0-13.8 Gy). Without adaptive replanning, target coverage would have been compromised in 2 cases (57% and 82% coverage without adaptation vs 100% for both with adaptation); neither patient experienced local failure. Radiation-related grade 3 toxicity rates were similar between groups.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Zhang X, Li Y, Pan X, et al. Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: a virtual clinical study. *Int J Radiat Oncol Biol Phys.* 2010;77(2):357-366.	Observational-Tx	20 patients	To compare dose volume histograms of intensity-modulated proton therapy with those of IMRT and passive scattering proton therapy for the treatment of stage IIIB NSCLC and to explore the possibility of individualized radical RT.	Compared with IMRT, intensity-modulated proton therapy spared more lung, heart, spinal cord, and esophagus, even with dose escalation from 63 Gy to 83.5 Gy, with a mean maximum tolerated dose of 74 Gy. Compared with passive scattering proton therapy, intensity-modulated proton therapy allowed further dose escalation from 74 Gy to a mean maximum tolerated dose of 84.4 Gy (range, 79.4-88.4 Gy) while all parameters of normal tissue sparing were kept at lower or similar levels. In addition, intensity-modulated proton therapy prevented lower-dose target coverage in patients with complicated tumor anatomies.	3
33. 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	78 patients randomized to the chemotherapy-RT group and 77 randomized to the RT group	To provide data for 7 years of follow-up of patients enrolled in the CALGB trial.	There were 78 eligible patients randomly assigned to the chemotherapy-RT group and 77 randomly assigned to the RT group. Both groups were similar in terms of sex, age, histologic cell type, performance status, substage of disease, and whether staging had been clinical or surgical. All patients had measurable or evaluable disease at the time of random assignment to treatment groups. Both groups received a similar quantity and quality of RT. As previously reported, the rate of tumor response, as determined radiographically, was 56% for the chemotherapy-RT group and 43% for the RT group (P=.092). After more than 7 years of follow-up, the median survival remains greater for the chemotherapy-RT (13.7 months) than for the RT group (9.6 months) (P=.012) as ascertained by the log-rank test (two-sided). The percentages of patients surviving after years 1 through 7 were 54, 26, 24, 19, 17, 13, and 13 for the chemotherapy-RT group and 40, 13, 10, 7, 6, 6, and 6 for the RT group.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small cell lung carcinoma. *Lung Cancer.* 1994;10 Suppl 1:S239-244.	Experimental-Tx	353 total patients: 177 patients received RT alone, and 176 received the combined treatment	To report the results of a large randomized study comparing RT alone to combined RT and chemotherapy in unresectable squamous cell and large cell lung carcinoma.	The 2-year survival rate was 14% for patients receiving RT vs 21% for patients receiving the combined treatment (P=0.02). The distant metastasis rate was significantly lower in the group receiving the combined treatment (P<0.001). Local control at 1 year was poor in both groups (17% and 15%, respectively) and remains a major problem in locally advanced NSCLC.	1
35. Sause W, Kolesar P, Taylor SI, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest.* 2000;117(2):358-364.	Experimental-Tx	458 patients	To test whether chemotherapy followed by RT resulted in superior survival to either hyperfractionated radiation or standard radiation in surgically unresectable NSCLC.	OS was statistically superior for the patients receiving chemotherapy and radiation vs the other 2 arms of the study. The twice-daily RT arm, although better, was not statistically superior in survival for those patients receiving standard radiation. Median survival for standard radiation was 11.4 months; for chemotherapy and RT, 13.2 months; and for hyperfractionated RT, 12 months. The respective 5-year survivals were 5% for standard RT, 8% for chemotherapy followed by RT, and 6% for hyperfractionated RT.	1
36. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med.* 1992;326(8):524-530.	Experimental-Tx	331 patients	Randomized study to examine the effects of concomitant cisplatin and RT on inoperable NSCLC.	Survival was significantly improved in the RT-daily-cisplatin group as compared with the RT group (P=0.009): survival in the RT-daily-cisplatin group was 54% at 1 year, 26% at 2 years, and 16% at 3 years, as compared with 46%, 13%, and 2%, respectively, in the RT group. Survival in the RT-weekly-cisplatin group was intermediate (44%, 19%, and 13%) and not significantly different from survival in either of the other 2 groups. The survival benefit of daily combined treatment was due to improved control of local disease (P=0.003). Survival without local recurrence was 59% at 1 year and 31% at 2 years in the RT-daily-cisplatin group; 42% and 30%, respectively, in the RT-weekly-cisplatin group; and 41% and 19%, respectively, in the RT group. Cisplatin induced nausea and vomiting in 86% of the patients given it weekly and in 78% of those given it daily; these effects were severe in 26% and 28%, respectively.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *Bmj.* 1995;311(7010):899-909.	Review/Other-Tx	9,387 patients (7,151 deaths) from 52 randomized clinical trials	To evaluate the effect of cytotoxic chemotherapy on survival in patients with NSCLC.	The results for modern regimens containing cisplatin favored chemotherapy in all comparisons and reached conventional levels of significance when used with radical RT and with supportive care. Trials comparing surgery with surgery plus chemotherapy gave a HR of 0.87 (13% reduction in the risk of death, equivalent to an absolute benefit of 5% at 5 years). Trials comparing radical RT with radical RT plus chemotherapy gave a HR of 0.87 (13% reduction in the risk of death; absolute benefit of 4% at 2 years), and trials comparing supportive care with supportive care plus chemotherapy 0.73 (27% reduction in the risk of death; 10% improvement in survival at 1 year). The essential drugs needed to achieve these effects were not identified. No difference in the size of effect was seen in any subgroup of patients. In all but the radical RT setting, older trials using long term alkylating agents tended to show a detrimental effect of chemotherapy. This effect reached conventional significance in the adjuvant surgical comparison.	4

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis. *Cancer.* 1995;76(4):593-601.	Review/Other-Tx	14 trials; 1,887 patients	To perform a meta-analysis study using clinical trials that evaluated combined RT plus chemotherapy vs RT alone in patients with stages IIIa and IIIb NSCLC.	Survival probabilities at 1, 2, 3, and 5 years, as estimated from published survival curves, were considered as the endpoints of interest. For survival at 3 and 5 years, the point estimates and the CIs were used. Quality scoring of the studies also was performed. 14 trials were selected, comprising 1,887 patients in the meta-analysis. For the cisplatin-based group, the estimated pooled odds ratio of death at 1 and 2 years was 0.76 (0.6-0.9 CI) and 0.70 (0.5-0.9 CI), with a reduction in mortality of 24% and 30%, respectively. For the noncisplatin-based group, the estimated pooled odds ratio at 1 and 2 years was 1.05 (0.7-1.5 CI) and 0.82 (0.5-1.3 CI), with a reduction in mortality of 5% and 18%, respectively. However, no significant differences were found between the percentage of survival and the CI at 3 and 5 years using the point estimates.	4
39. Auperin A, Le Pechoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol.* 2006;17(3):473-483.	Review/Other-Tx	9 trials; 1,764 patients	To undertake a meta-analysis based on all available individual patient data from randomized trials to determine whether concomitant chemotherapy might lead to a moderate improvement in survival in patients with locally advanced NSCLC.	There were 12 eligible trials that included a total of 1,921 patients. The data from 3 trials were not available. Therefore, the analysis was based on 9 trials including 1,764 patients. Median follow-up was 7.2 years. The HR of death among patients treated with radio-chemotherapy compared to RT alone was 0.89 (95% CI, 0.81–0.98; P=0.02) corresponding to an absolute benefit of chemotherapy of 4% at 2 years. There was some evidence of heterogeneity among trials and sensitivity analyses did not lead to consistent results. The combination of platin with etoposide seemed more effective than platin alone.	4

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Bonner JA, McGinnis WL, Stella PJ, et al. The possible advantage of hyperfractionated thoracic radiotherapy in the treatment of locally advanced nonsmall cell lung carcinoma: results of a North Central Cancer Treatment Group Phase III Study. *Cancer.* 1998;82(6):1037-1048.	Experimental-Tx	99 patients	To compare response rates, time to local or distant progression, and survival for patients with unresectable (stage IIIA or IIIB) NSCLC treated with standard fractionated TRT vs accelerated hyperfractionated TRT with or without combination etoposide and cisplatin chemotherapy.	This article reports mature follow-up, because more than 80% of the patients have died. The median follow-up of living patients was 2.5 years. There were suggestions of improvement in the rates of freedom from local recurrence and survival for patients treated with accelerated hyperfractionated TRT (with or without chemotherapy) as opposed to standard fractionated TRT (P=0.06 and P=0.10, respectively). The improvement in survival associated with accelerated hyperfractionated TRT (with or without chemotherapy) was statistically significant for the subgroup of patients with nonsquamous cell carcinoma after adjustment for other potentially confounding factors (P=0.02). No differences in freedom from systemic progression or survival were found in a comparison of accelerated hyperfractionated TRT with chemotherapy and accelerated hyperfractionated TRT without chemotherapy.	1
41. Schild SE, Stella PJ, Geyer SM, et al. Phase III trial comparing chemotherapy plus once-daily or twice-daily radiotherapy in Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2002;54(2):370-378.	Experimental-Tx	234 patients	To determine whether chemotherapy plus b.i.d. or q.d. RT resulted in superior survival for patients with stage III NSCLC.	Of the 234 patients, 123 had stage IIIa disease and 111 had stage IIIb disease. The incidence of severe (Grade 3 or greater) acute nonhematologic toxicity (q.d. RT, 53% vs b.i.d. RT, 65%) and severe (Grade 3 or greater) hematologic toxicities (thrombocytopenia, 41% q.d. RT vs 39% b.i.d. RT; neutropenia, 80% q.d. RT vs 81% b.i.d. RT) was not significantly different between the treatment arms. Five patients (3 in q.d. RT group and 2 in b.i.d. RT group) died as a result of acute toxicity. The follow-up ranged from 2 to 73 months (median 43). No significant differences were found between the q.d. and b.i.d. RT arms in terms of time to progression (P=0.9; median 9.4 and 9.6 months, respectively), OS (P=0.4; median 14 and 15 months and 2-year survival rate 37% and 40%, respectively), and cumulative incidence of local failure (P=0.6; 2-year rate 45% and 41%, respectively).	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Movsas B, Scott C, Langer C, et al. Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: radiation therapy oncology group trial 98-01. *J Clin Oncol.* 2005;23(10):2145-2154.	Experimental-Tx	243 patients	To test the ability of the cytoprotectant, amifostine, to reduce chemoradiotherapy-induced esophagitis and evaluate its influence on QOL and swallowing symptoms.	A total of 120 patients were randomly assigned to receive amifostine, and 122, to receive no amifostine (one patient was ineligible); 72% received amifostine per protocol or with a minor deviation. Amifostine was associated with higher rates of acute nausea (P=.03), vomiting (P=.007), cardiovascular toxicity (P=.0001), and infection or febrile neutropenia (P=.03). The rate of ≥grade 3 esophagitis was 30% with amifostine vs 34% without amifostine (P=.9). Patient diaries demonstrated lower swallowing dysfunction area under the curve with amifostine (z test P=.025). QOL was not significantly different between the 2 arms, except for pain, which showed more clinically meaningful improvement and less deterioration at 6 weeks follow-up (vs pretreatment) in the amifostine arm (P=.003). The median survival rates for both arms were comparable (amifostine, 17.3 vs no amifostine, 17.9 months; P=.87).	1
43. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol.* 1999;17(9):2692-2699.	Experimental-Tx	320 patients	To determine whether concurrent or sequential treatment with RT and chemotherapy improves survival in unresectable stage III NSCLC.	Pretreatment characteristics were well balanced between the treatment arms. The response rate for the concurrent arm was significantly higher (84.0%) than that of the sequential arm (66%) (P=.0002). The median survival duration was significantly superior in patients receiving concurrent therapy (16.5 months), as compared with those receiving sequential therapy (13.3 months) (P=.03998). 2-, 3-, 4-, and 5-year survival rates in the concurrent group (34.6%, 22.3%, 16.9%, and 15.8%, respectively) were better than those in the sequential group (27.4%, 14.7%, 10.1%, and 8.9%, respectively). Myelosuppression was significantly greater among patients on the concurrent arm than on the sequential arm (P=.0001).	1

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Francais de Pneumo-Cancerologie NPC 95-01 Study. *J Clin Oncol.* 2005;23(25):5910-5917.	Experimental-Tx	205 patients	Phase III study was performed to compare the survival impact of concurrent vs sequential treatment with RT and chemotherapy in unresectable stage III NSCLC.	Pretreatment characteristics were well balanced between the 2 arms. There were 6 toxic deaths in the sequential arm and 10 in the concurrent arm. Median survival was 14.5 months in the sequential arm and 16.3 months in the concurrent arm (log-rank test P=.24). 2-, 3-, and 4-year survival rates were better in the concurrent arm (39%, 25%, and 21%, respectively) than in the sequential arm (26%, 19%, and 14%, respectively). Esophageal toxicity was significantly more frequent in the concurrent arm than in the sequential arm (32% vs 3%).	1
45. Rowell NP, O'Rourke N P. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev.* 2004(4):CD002140.	Review/Other-Tx	14 randomized studies (2,393 patients)	To determine the effectiveness of concurrent chemoradiotherapy as compared to RT alone with regard to local control and OS; and to determine whether the addition of concurrent chemotherapy results in an altered risk of treatment-related morbidity. To compare concurrent with sequential chemoradiotherapy.	In a meta-analysis there was a reduction in risk of death at two years (RR 0.93; 95% CI, 0.88 to 0.98; P=0.01). Similar improvements in 2-year locoregional PFS (RR 0.84; 95% CI, 0.72 to 0.98; P=0.03) and PFS at any site (RR 0.90; 95% CI, 0.84 to 0.97; P=0.005) were also seen in those receiving concurrent chemoradiotherapy. Subgroup analysis suggested the possibility of a greater benefit from regimens which incorporated once daily fractionation of RT or a higher total chemotherapy dose. The incidence of acute esophagitis, neutropenia and anemia were significantly increased by concurrent chemoradiotherapy. In a meta-analysis of 3 trials of concurrent vs sequential chemoradiotherapy there was a significant reduction in the risk of death at 2 years with concurrent treatment (RR 0.86; 95% CI, 0.78 to 0.95; P=0.003) but potentially at the expense of toxicity, although data was incomplete.	4

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol.* 2010;28(13):2181-2190.	Review/Other-Tx	6 trials (1,205 patients)	A meta-analysis of randomized trials directly comparing concomitant vs sequential radiochemotherapy.	Median follow-up was 6 years. There was a significant benefit of concomitant radiochemotherapy on OS (HR, 0.84; 95% CI, 0.74 to 0.95; P=.004), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years. For PFS, the HR was 0.90 (95% CI, 0.79 to 1.01; P=.07). Concomitant treatment decreased locoregional progression (HR, 0.77; 95% CI, 0.62 to 0.95; P=.01); its effect was not different from that of sequential treatment on distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; P=.69). Concomitant radiochemotherapy increased acute esophageal toxicity (grade 3-4) from 4% to 18% with a RR of 4.9 (95% CI, 3.1 to 7.8; P=.001). There was no significant difference regarding acute pulmonary toxicity.	4
47. Schild SE, McGinnis WL, Graham D, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2006;65(4):1106-1111.	Observational-Tx	15 patients	To determine the maximum tolerated dose of radiation that can be administered with carboplatin and paclitaxel.	2 patients were not evaluable because they did not receive therapy according to the protocol. No dose-limiting toxicity occurred in the 3 patients who received 70 Gy, 1 dose-limiting toxicity occurred in the 6 patients who received 74 Gy, and 2 dose-limiting toxicity occurred in the 4 patients who received 78 Gy. The dose-limiting toxicity included Grade 3 pneumonitis (n=2) and Grade 4 pneumonitis (n=1). There have been 3 deaths during follow-up ranging from 14 to 38 months (median, 28 months).	2
48. Socinski MA, Rosenman JG, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B nonsmall cell lung carcinoma: a modified phase I/II trial. *Cancer.* 2001;92(5):1213-1223.	Observational-Tx	62 patients	To assess the feasibility, toxicity, and impact on clinical outcomes of dose-escalating conformal TRT with induction and concurrent carboplatin/paclitaxel and provide a more mature evaluation of this approach in unresectable stage IIIA/B NSCLC.	The response rate to induction carboplatin/paclitaxel was 40%. 8 patients (13%) progressed on the induction phase. No dose-limiting toxicity was observed during the escalation of the TRT dose from 60 to 74 Gy. The major toxicity was esophagitis; however, only 8% developed Grade 3/4 esophagitis using RTOG criteria. The overall response rate was 52%. Survival rates at 1, 2, 3, and 4 years were 71%, 52%, 40%, and 36%, respectively, with a median survival of 26 months. The 1-, 2-, and 3-year PFS probabilities were 47%, 35%, and 29%, respectively.	2

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Bradley JD, Graham MV, Moughan J, et al. Phase I/II results of RTOG L-0117; a phase I/II dose intensification study using 3DCRT and concurrent chemotherapy for patients with inoperable NSCLC: PD5-2-4. *Journal of Thoracic Oncology.* 2007;2(8):S476.	Observational-Tx	Phase I-17 patients; Phase II-31 patients	Phase I/II study was initiated to establish the maximum tolerated dose of RT, in the setting of concurrent chemotherapy, using 3D-CRT for NSCLC.	The phase I portion of this study accrued 17 patients from 8 institutions and was closed in January 2004. After the initial 8 patients were accrued to Arm 1, the trial closed temporarily on September 26, 2002 due to reported toxicity. Two acute treatment related dose-limiting toxicity was reported: a grade 5 infection/febrile neutropenia and a grade 3 pneumonitis. The protocol, therefore, was revised to de-escalate the RT dose (74 Gy/37 fractions). Arm 2 accrued 9 patients with 2 (22%) developing Grade 3 gastrointestinal toxicities and 1 (11%) reporting a Grade 3 infection/febrile neutropenia. Phase II has accrued 31 eligible patients at 74 Gy. Of the 27 (87%) patients with acute toxicity information, there were 3 (11%) Grade 3 pain toxicities, 2 (7%) Grade 3 infection/febrile neutropenia toxicities, 1 (4%) Grade 3 pulmonary toxicity and 1 (4%) Grade 3 skin toxicity. A total of 13 (48%) patients reported grade 3+ non-hematologic toxicities.	3
50. 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 patients	To evaluate whether induction chemotherapy before concurrent chemoradiotherapy would result in improved survival.	34% of patients were female, 66% were male, and the median age was 63 years. Grade 3 or 4 toxicities during induction chemotherapy on arm B consisted mainly of neutropenia (18% and 20%, respectively). During concurrent chemoradiotherapy, there was no difference in severity of in-field toxicities of esophagitis (grade 3 and 4 were, respectively, 30% and 2% for arm A vs 28% and 8% for arm B) and dyspnea (grade 3 and 4 were, respectively, 11% and 3% for arm A vs 15% and 4% for arm B). Survival differences were not statistically significant (P=.3), with a median survival on arm A of 12 months (95% CI, 10-16 months) vs 14 months (95% CI, 11-16 months) on arm B and a 2-year survival of 29% (95% CI, 22%-35%) and 31% (95% CI, 25%-38%). Age, weight loss before therapy, and performance status were statistically significant predictive factors.	1

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. 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	To determine the optimal sequencing and integration of paclitaxel/carboplatin with standard daily TRT, in patients with locally advanced unresected stage III NSCLC.	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 TRT was esophagitis, which was more pronounced with the administration of concurrent chemoradiotherapy on study arms 2 and 3 (19% and 28%, respectively).	1
52. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol.* 2003;21(10):2004-2010.	Observational-Tx	83 patients	To test the concept of taxane sequencing in combined-modality therapy, this phase II trial (S9504) evaluated consolidation docetaxel after concurrent chemoradiotherapy in patients with pathologically documented stage IIIB NSCLC.	Stage subsets (tumor-node-metastasis system) in 83 eligible patients were as follows: T4N0/1, 31 patients (37%); T4N2, 22 patients (27%), and T1-3N3, 30 patients (36%). Concurrent chemoradiotherapy was generally well tolerated, but 2 patients died from probable radiation-associated pneumonitis. Neutropenia during consolidation docetaxel was common (57% with grade 4) and most frequent during escalation to 100 mg/m2. Median PFS was 16 months, median survival was 26 months, and 1-, 2-, and 3-year survival rates were 76%, 54%, and 37%, respectively. Brain metastasis was the most common site of failure. In S9019, median survival was 15 months and 1-, 2-, and 3-year survival rates were 58%, 34%, and 17%, respectively.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol.* 2008;26(35):5755-5760.	Experimental-Tx	203 patients	Randomized phase III trial to evaluate whether consolidation docetaxel after cisplatin, etoposide, and RT resulted in a median survival time of 26 months.	On the basis of evidence of futility, a data and safety monitoring board recommended early termination after an analysis of the initial 203 patients. Patient characteristics (n=203) were as follows: 34% female; median age, 63 years; 39.4% stage IIIA; and 60.6% stage IIIB. 147 (72.4%) of 203 patients were randomly assigned to docetaxel (n=73) or observation (n=74). Grade 3 to 5 toxicities during docetaxel included febrile neutropenia (10.9%) and pneumonitis (9.6%); 28.8% of patients were hospitalized during docetaxel (vs 8.1% in observation arm), and 5.5% died as a result of docetaxel. The median survival time for all patients (n=203) was 21.7 months; median survival time was 21.2 months for docetaxel arm compared with 23.2 months for observation arm (P=.883).	1
54. 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 of patients with previously untreated, potentially resectable clinical stage IIIA NSCLC to compare the results of perioperative chemotherapy and surgery with those of surgery alone.	After 3 cycles of preoperative chemotherapy, the rate of clinical major response was 35%. Patients treated with perioperative chemotherapy and surgery had an estimated median survival of 64 months compared with 11 months for patients who had surgery alone (P<.008 by log-rank test; P<.018 by Wilcoxon test). The 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.	1
55. Blumenschein GR, Jr., Paulus R, Curran WJ, et al. Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. *J Clin Oncol.* 2011;29(17):2312-2318.	Observational-Tx	87 patients	The authors report a phase II trial testing the combination of cetuximab with chemoradiotherapy in unresectable stage III NSCLC.	Median follow-up was 21.6 months. Response rate was 62% (n=54), median survival was 22.7 months, and 24-month OS was 49.3%. Adverse events related to treatment included 20% grade 4 hematologic toxicities, 8% grade 3 esophagitis, and 7% grade 3 to 4 pneumonitis. There were 5 grade 5 events.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
56. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol.* 2008;26(15):2450-2456.	Experimental-Tx	243 patients randomized	The authors hypothesized that the introduction of gefitinib after maximum cytoreduction with chemoradiotherapy for stage III NSCLC would prolong PFS and extend OS.	An unplanned interim analysis conducted in April 2005 rejected the alternative hypothesis of improved survival at the P=.0015 level for 243 randomly assigned patients closed, and preliminary results were reported. With a median follow-up time of 27 months, median survival time was 23 months for gefitinib (n=118) and 35 months for placebo (n=125; two-sided P=.013). The toxic death rate was 2% with gefitinib compared with 0% for placebo.	1
57. Movsas B, Moughan J, Sarna L, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. *J Clin Oncol.* 2009;27(34):5816-5822.	Experimental-Tx	243 patients	To test the ability of the cytoprotectant, amifostine, to reduce chemoradiotherapy-induced esophagitis and evaluate its influence on QOL and swallowing symptoms.	A total of 120 patients were randomly assigned to receive amifostine, and 122, to receive no amifostine (1 patient was ineligible); 72% received amifostine per protocol or with a minor deviation. Amifostine was associated with higher rates of acute nausea (P=.03), vomiting (P=.007), cardiovascular toxicity (P=.0001), and infection or febrile neutropenia (P=.03). The rate of ≥grade 3 esophagitis was 30% with amifostine vs 34% without amifostine (P=.9). Patient diaries demonstrated lower swallowing dysfunction area under the curve with amifostine (z test P=.025). QOL was not significantly different between the 2 arms, except for pain, which showed more clinically meaningful improvement and less deterioration at 6 weeks follow-up (vs pretreatment) in the amifostine arm (P=.003). The median survival rates for both arms were comparable (amifostine, 17.3 vs no amifostine, 17.9 months; P=.87).	1

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Ready N, Janne PA, Bogart J, et al. Chemoradiotherapy and gefitinib in stage III non-small cell lung cancer with epidermal growth factor receptor and KRAS mutation analysis: cancer and leukemia group B (CALEB) 30106, a CALGB-stratified phase II trial. *J Thorac Oncol.* 2010;5(9):1382-1390.	Experimental-Tx	63 patients	To determine whether adding gefitinib to sequential or concurrent CRT improved outcome in nonsurgical stage III NSCLC.	Acute high-grade infield toxicities were not clearly increased compared with historical CRT data. Poor-risk (n = 21) median PFS was 13.4 months (95% CI, 6.4–25.2) and median OS 19.0 months (95% CI, 9.9–28.4). Good-risk (n = 39) median PFS was 9.2 months (95% CI, 6.7–12.2), and median OS was 13 months (95% CI, 8.5–17.2). 13/45 tumors analyzed had activating EFGR mutations, and 2/13 also had T790M mutations. 7 tumors of 45 had KRAS mutations. There was no apparent survival difference with EGFR-activating mutations versus wild type or KRAS mutation versus wild type.	1
59. Bradley J, Masters GA, Hu CS, et al. RTOG 0617: Standard or High-Dose Radiation With or Without Cetuximab. Paper presented at: 15th World Conference on Lung Cancer; October 27-30, 2013; Sydney, Australia.	Experimental-Tx	544 patients	To present results of the RTOG 0617 trial comparing OS differences between standard-dose (60 Gy) and high-dose (74 Gy) RT with concurrent chemotherapy and comparing standard chemoradiotherapy with the addition of cetuximab in an unselected population.	Median survival was 23.1 versus 23.5 months, and 18-month OS was 60.8% and 60.2% for cetuximab compared with no cetuximab, respectively (P=.484; HR = 0.99), which crossed a protocol-specified futility boundary for early reporting. Median survival was 28.7 months versus 19.5 months, and 18-month OS was 66.9% versus 53.9% for standard-dose and high-dose RT, respectively (P=.0007; HR = 1.56).	1
60. National Cancer Institute (NCI). A Randomized Phase II Study of Individualized Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer (NSCLC). In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). December 12, 2013. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01822496?term=NCT01822496&rank=1. NLM Identifier: NCT01822496.	Review/Other-Tx	N/A	Randomized phase II trial to study how well giving erlotinib hydrochloride or crizotinib and chemoradiation therapy works in treating patients with stage III NSCLC.	This trial is not yet open for participant recruitment and results are not available yet.	4

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
61. Massachusetts General Hospital. Afatinib Sequenced With Concurrent Chemotherapy and Radiation in EGFR-Mutant Non-Small Cell Lung Tumors: The ASCENT Trial. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). December 12, 2013. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01553942?term=NCT01553942&rank=1. NLM Identifier: NCT01553942.	Review/Other-Tx	Ongoing	To determine if adding afatinib to standard treatment helps to improve the response to treatment in patients with stage III NSCLC and EGFR mutations.	This trial is still recruiting study subjects and results are not available yet.	4
62. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol.* 2005;23(25):5900-5909.	Experimental-Tx	1,079 patients	To examine the influence of somatic EGFR and KRAS mutations on the clinical outcome of patients with advanced NSCLC.	EGFR mutations were detected in 13% of tumors and were associated with longer survival, irrespective of treatment (P<.001). Among erlotinib-treated patients, EGFR mutations were associated with improved response rate (P<.05) and there was a trend toward an erlotinib benefit on time to progression (P=.092), but not improved survival (P=.96). KRAS mutations (21% of tumors) were associated with significantly decreased time to progression and survival in erlotinib plus chemotherapy-treated patients.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
63. 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	To determine whether adjuvant vinorelbine plus cisplatin prolongs OS among patients with completely resected early-stage NSCLC.	A total of 482 patients underwent randomization to vinorelbine plus cisplatin (242 patients) or observation (240); 45% of the patients had pathological stage IB disease and 55% had stage II, and all had an ECOG performance status score of 0 or 1. In both groups, the median age was 61 years, 65% were men, and 53% had adenocarcinomas. Chemotherapy caused neutropenia in 88% of patients (including grade 3 febrile neutropenia in 7%) and death from toxic effects in 2 patients (0.8%). Nonhematologic toxic effects of chemotherapy were fatigue (81% of patients), nausea (80%), anorexia (55%), vomiting (48%), neuropathy (48%), and constipation (47%), but severe (grade 3 or greater) toxic effects were uncommon (<10%). OS was significantly prolonged in the chemotherapy group as compared with the observation group (94 vs 73 months; HR for death, 0.69; P=0.04), as was relapse-free survival (not reached vs 46.7 months; HR for recurrence, 0.60; P<0.001). 5-year survival rates were 69% and 54%, respectively (P=0.03).	1
64. Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. *PLoS Med.* 2005;2(1):e17.	Observational-Tx	60 lung adenocarcinomas	To determine whether mutations in KRAS could be used to further enhance prediction of response to gefitinib or erlotinib.	9/38 (24%) tumors refractory to either kinase inhibitor had KRAS mutations, while 0/21 (0%) drug-sensitive tumors had such mutations (P=0.02). The 95% CIs for these observations are 13%–39% and 0%–16%, respectively. Conversely, 17/22 (77%) tumors sensitive to either kinase inhibitor had EFGR mutations, in contrast to 0/38 (0%) drug-resistant tumors (P=6.8 3 10 11). The 95% CIs for these observed response rates are 57%–90% and 0%–9%, respectively. All 17 tumors with EFGR mutations responded to gefitinib or erlotinib, while all 9 tumors with KRAS mutations did not (P=3.2 3 10 7). Results suggest that treatment decisions regarding use of these kinase inhibitors might be improved by determining the mutational status of both EFGR and KRAS.	2

Nonsurgical Treatment for Locally Advanced NSCLC-Good Performance Status Definitive Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
65. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* 2005;353(2):123-132.	Experimental-Tx	731 patients	Randomized, placebo-controlled, double-blind trial to determine whether the EFGR inhibitor erlotinib prolongs survival in NSCLC after the failure of first-line or second-line chemotherapy.	The response rate was 8.9% in the erlotinib group and <1% in the placebo group (P<0.001); the median duration of the response was 7.9 months and 3.7 months, respectively. PFS was 2.2 months and 1.8 months, respectively (HR, 0.61, adjusted for stratification categories; P<0.001). OS was 6.7 months and 4.7 months, respectively (HR, 0.70; P<0.001), in favor of erlotinib. 5% of patients discontinued erlotinib because of toxic effects.	1
66. Ramalingam SS, Dahlberg SE, Langer CJ, et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. *J Clin Oncol.* 2008;26(1):60-65.	Observational-Tx	224 patients	A subset analysis of ECOG 4599 was performed to determine the outcome for elderly, advanced-stage NSCLC patients treated with bevacizumab in combination with carboplatin and paclitaxel.	Among elderly patients (n=224; 26%), there was a trend towards higher response rate (29% vs 17%; P=.067) and PFS (5.9 vs 4.9 months; P=.063) with bevacizumab in combination with carboplatin and paclitaxel compared with paclitaxel and carboplatin, although OS (bevacizumab in combination with carboplatin and paclitaxel = 11.3 months; paclitaxel and carboplatin = 12.1 months; P=.4) was similar. Grade 3 to 5 toxicities occurred in 87% of elderly patients with bevacizumab in combination with carboplatin and paclitaxel vs 61% with paclitaxel and carboplatin (P<.001), with 7 treatment-related deaths in the bevacizumab in combination with carboplatin and paclitaxel arm compared with 2 with paclitaxel and carboplatin. Elderly patients had higher incidence of grade 3 to 5 neutropenia, bleeding, and proteinuria with bevacizumab in combination with carboplatin and paclitaxel compared with younger patients.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
67. Socinski MA, Stinchcombe TE, Moore DT, et al. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. *J Clin Oncol.* 2012;30(32):3953-3959.	Observational-Tx	45 patients	To incorporate bevacizumab and erlotinib agents with induction and concurrent chemoradiotherapy in stage III NSCLC.	The objective response rates to induction and overall treatment were 39% (95% CI, 24%–55%) and 60% (95% CI, 44%–75%), respectively. The median PFS and OS times were 10.2 months (95% CI, 8.4–18.3 months) and 18.4 months (95% CI, 13.4–31.7 months), respectively. The principal toxicity was esophagitis (29% grade 3 or 4 esophagitis, with 1 patient with grade 3 tracheoesophageal fistula), which was often prolonged. Consolidation therapy with bevacizumab and erlotinib was not feasible.	1
68. 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 patients assigned to group 1 and 194 assigned to group 2	Phase III trial was performed to compare concurrent chemotherapy and RT followed by resection with standard concurrent chemotherapy and definitive RT without resection.	Median OS was 23.6 months (IQR 9.0-not reached) in group 1 vs 22.2 months (9.4-52.7) in group 2 (HR 0.87 [0.70-1.10]; P=0.24). Number of patients alive at 5 years was 37 (point estimate 27%) in group 1 and 24 (point estimate 20%) in group 2 (odds ratio 0.63 [0.36-1.10]; P=0.10). With N0 status at thoracotomy, the median OS was 34.4 months (IQR 15.7-not reached; 19 [point estimate 41%] patients alive at 5 years). 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), HR 0.77 [0.62-0.96]; P=0.017); the number of patients without disease progression at 5 years was 32 (point estimate 22%) vs 13 (point estimate 11%), respectively. 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). In group 1, 16 (8%) deaths were treatment related vs 4 (2%) in group 2. In an exploratory analysis, OS was improved for patients who underwent lobectomy, but not pneumonectomy, vs chemotherapy plus RT.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
69. Stinchcombe TE, Lee CB, Moore DT, et al. Long-term follow-up of a phase I/II trial of dose escalating three-dimensional conformal thoracic radiation therapy with induction and concurrent carboplatin and paclitaxel in unresectable stage IIIA/B non-small cell lung cancer. *J Thorac Oncol.* 2008;3(11):1279-1285.	Observational-Tx	62 patients	A modified phase I/II trial was performed to investigate the incorporation of 3D-CRT into the treatment paradigm of induction and concurrent carboplatin and paclitaxel in patients with unresectable stage IIIA/B NSCLC.	With a median follow-up for survivors of approximately 9 years (range, 7-11 years) the median PFS, time to tumor progression, and OS (with 95% CIs) were 10 (8.5-17), 15 (9-50), and 25 months (18-37), respectively. The 5-year PFS and OS rates were 21% (12%-32%) and 27% (17%-39%), respectively. The 10-year OS rate was 14% (7%-25%).	2
70. Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer.* 2004;46(1):87-98.	Experimental-Tx	102 patients	To compare the safety and efficacy of concurrent and sequential chemoradiotherapy, with chemotherapy consisting of a cisplatin and vinorelbine regimen, in patients with locally advanced NSCLC.	OS was significantly longer in arm A (median survival 16.6 months) vs arm B (median survival 12.9 months) (P=0.023 by means of log-rank test; HR = 0.61, 95% CI of HR (0.39-0.93)), and time to progression was also significantly longer in arm A (median time to progression 11.9 months) vs arm B (median time to progression 8.5 months) (P=0.024 by means of log-rank test; HR = 0.62, 95% CI of HR (0.38-0.93)). 98 patients were evaluable for response and 101 for toxicity. The overall response rate was significantly higher in arm A, 80% (with 21% complete response) compared with 47% (with 17% complete response) in arm B (P=0.001 by means of chi(2)-test). WHO grade 3 or 4 toxicity was more frequent in arm A than in arm B, with a significantly greater incidence of leucopenia (53% vs 19%, P=0.009 by means of chi(2) test) and nausea/vomiting (39% vs 15%, P=0.044 by means of chi(2) test). There were no treatment related deaths.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. Huber RM, Flentje M, Schmidt M, et al. Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non-small-cell lung cancer: study CTRT99/97 by the Bronchial Carcinoma Therapy Group. *J Clin Oncol.* 2006;24(27):4397-4404.	Experimental-Tx	212 patients	To examine whether, after preceding induction chemotherapy, simultaneous chemoradiotherapy is superior to RT alone.	Median follow-up time of all randomly assigned patients was 13.6 months (IQR, 6.4 to 29.0 months), and median follow-up time of the subgroup of censored patients (n=52) was 37.4 months (IQR, 5.9 to 57.0 months; maximum, 76.1 months). Toxicities during the induction phase were mild. During RT, overall toxicity rates were not significantly different between the 2 arms. Median survival times in the RT group and chemoradiotherapy group were 14.1 months (95% CI, 11.8-16.3 months) and 18.7 months (95% CI, 14.1-23.3 months; difference not statistically significant, P=.091). Median time to progression significantly favored simultaneous chemoradiotherapy (11.5 months; 95% CI, 8.3-14.7 months) vs RT alone (6.3 months; 95% CI, 5.0-7.6 months; P<.001, log-rank test).	1
72. Belderbos J, Uitterhoeve L, van Zandwijk N, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). *Eur J Cancer.* 2007;43(1):114-121.	Experimental-Tx	158 patients	Randomized phase III study was performed comparing sequential and concurrent chemoradiotherapy in NSCLC patients.	Acute hematological toxicity grade 3/4 was more pronounced in the sequential (30% vs 6%), esophagitis grade 3/4 more frequent in the concurrent arm (5% vs 14%). Late esophagitis grade 3 was 4% (sequential and concurrent), pneumonitis grade 3/4 14% (sequential) and 18% (concurrent). Because of the poor power of the study no significant differences in median survival, OS and PFS could be detected. Median survival was 16.2 (sequential) and 16.5 (concurrent) months, 2-year OS was 34% (sequential) and 39% (concurrent), 3-year OS was 22% (sequential) and 34% (concurrent).	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
73. Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. *J Clin Oncol.* 2008;26(15):2457-2463.	Experimental-Tx	62 patients	A modified phase I/II trial was conducted to evaluate the incorporation of 3D-CRT into a strategy of sequential and concurrent carboplatin/paclitaxel in stage III unresectable NSCLC.	The response rate to induction carboplatin/paclitaxel was 40%. 8 patients (13%) progressed on the induction phase. No dose-limiting toxicity was observed during the escalation of the TRT dose from 60 to 74 Gy. The major toxicity was esophagitis; however, only 8% developed Grade 3/4 esophagitis using RTOG criteria. The overall response rate was 52%. Survival rates at 1, 2, 3, and 4 years were 71%, 52%, 40%, and 36%, respectively, with a median survival of 26 months. The 1-, 2-, and 3-year PFS probabilities were 47%, 35%, and 29%, respectively.	1
74. Bradley JD, Bae K, Graham MV, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. *J Clin Oncol.* 2010;28(14):2475-2480.	Observational-Tx	53 patients	To report the results of the phase II portion of RTOG 0117, giving 74 Gy with concurrent weekly paclitaxel and carboplatin.	Of the combined phase I/II enrollment, a total of 55 patients received 74 Gy, of whom 53 were evaluable. The median follow-up was 19.3 months (range, 0.9 to 57.9 months) for all patients and 25.4 months (range, 13.1 to 57.9 months) for those still alive. The median survival for all patients was 25.9 months. The percentage surviving at least 12 months was 75.5% (95% CI, 65.7%-85.2%). The median OS and PFS times for stage III patients (n=44) were 21.6 months and 10.8 months, respectively. OS and PFS rates at 12 months were 72.7% and 50.0%, respectively. 12 patients experienced grade ≥3 lung toxicity (2 patients had Grade 5 lung toxicity).	2

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

3D-CRT = 3D-confromal radiation therapy

ALK = Anaplastic lymphoma kinase

CI = Confidence interval

CT = Computed tomography

EFGR = Epidermal growth factor receptor

HR = Hazard ratio

IFRT = Involved-field radiotherapy

IMRT = Intensity-modulated radiotherapy

IQR = Interquartile range

NSCLC = Non-small-cell lung cancer

OS = Overall survival

PET/CT = Positron emission tomography/computed tomography

PFS = Progression-free survival

QOL = Quality of life

RR = Relative risk

RT = Radiation therapy

TRT = Thoracic radiation therapy