Nonsurgical Treatment for Non-Small-Cell Lung Cancer Poor Performance Status or Palliative Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Boring CC, Squires TS, Tong T. Cancer statistics, 1993. *CA Cancer J Clin* 1993; 43(1):7-26.	15	9 cancer registries; 10% of US population	To review the 1993 cancer statistics.	1993 estimated statistics for lung: Men: Lung cancer incidence – 17%, Lung cancer deaths – 34%. Women: Cancer incidence – 12%; Deaths – 22%.	4
2. Perez CA, Stanley K, Grundy G, et al. Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung: report by the Radiation Therapy Oncology Group. *Cancer* 1982; 50(6):1091-1099.	1	378 patients	Radiation Therapy Oncology Group (RTOG) randomized trial evaluating unresectable locally advanced NSCLC 40 Gy continuous vs 40 Gy split vs 50 Gy vs 60 Gy (continuous).	60 Gy superior to other doses for intrathoracic control and OS. 60 Gy 1year survival 42%, 3year survival 15%.	1
3. Haffty BG, Goldberg NB, Gerstley J, Fischer DB, Peschel RE. Results of radical radiation therapy in clinical stage I, technically operable non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1988; 15(1):69-73.	4	43 patients with stage I NSCLC	To review the clinical results of stage I NSCLC patients, that were medically inoperable.	The actuarial survival rate of the 43 clinical stage I patients was 36% at 3 years and 21% at 5 years. Intrathoracic failures occurred in 39% of the patients. Despite the fact that the continuous course group was similar to the split course group in terms of age, histology, and tumor extent, the continuous course patients had a lower thoracic failure rate (2/11) vs 15/32), a longer median survival (51.6 months vs 27 months), and a better actuarial 5-year survival rate (45% vs 12%) when compared to the split course patients. Using Cox regression analysis to compare survival curves, the continuous course group had a significantly better survival compared to the split course group (P=.04).	2

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4. Hayakawa K, Mitsuhashi N, Saito Y, et al. Limited field irradiation for medically inoperable patients with peripheral stage I non-small cell lung cancer. *Lung Cancer* 1999; 26(3):137-142.	4	36 patients	To discuss the elective irradiation of regional lymph nodes by analyzing the outcome of limited field irradiation for medically inoperable patients with peripheral stage I NSCLC.	The OS rates at 3 and 5 years were 42 and 23%, and disease-specific survival rates were 56 and 39% at 3 and 5 years, respectively. In 26 patients without the elective regional irradiation, disease-specific survival rates at 3 and 5 years were 53 and 40%, respectively, whereas they were 64 and 39% in 10 patients with the regional nodal irradiation. The cumulative 5-year local progression rate was 28%, and the overall progression rate was 60% at 5 years. High-dose limited field RT is justified for medically inoperable patients with peripheral stage I NSCLC. The regional nodal irradiation can be omitted in these pulmonary compromised patients because of the low regional relapse rate. Dose-escalation by a conformal RT with a small target volume can be expected to provide a better local control rate and better survival.	2
5. Kaskowitz L, Graham MV, Emami B, Halverson KJ, Rush C. Radiation therapy alone for stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1993; 27(3):517-523.	4	53 patients	Retrospective analysis to evaluate patients with stage I NSCLC treated with RT alone.	The actuarial OS rate for the entire group was 19% at 3 years and 6% at 5 years, with a MST of 20.9 months. Of the 49 deaths, 35 died of lung cancer; 13 died of intercurrent illness, and one died of pancreatic cancer, which made the actuarial cause-specific survival 33% at 3 years and 13% at 5 years. The actuarial 3-year DFS was 33%. Local primary tumor progression occurred in 22 patients, resulting in a 51% 3-year actuarial freedom from local progression. Multivariate analysis found only T stage to be associated with OS (P=.02). Multivariate analysis showed age as a prognostic factor to be approaching statistical significance (P=.07). Patients under 70 years of age showed an increased survival rate compared to patients over 70 years. RT doses ≥65 Gy appeared to result in a decreased proportion of patients dying of lung cancer with no apparent increase in either acute or long-term complication rates. Results of definitive RT for inoperable stage I NSCLC remain inferior to surgical therapy.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
6. Noordijk EM, vd Poest Clement E, Hermans J, Wever AM, Leer JW. Radiotherapy as an alternative to surgery in elderly patients with resectable lung cancer. *Radiother Oncol* 1988; 13(2):83-89.	4	50 patients	To review the clinical results of elderly (age >70) patients with poor pulmonary and/or cardiac function by using RT as alternative to surgery.	The crude OS rates were 56% at 2 years and 16% at 5 years, with a median survival of 27 months. Age did not influence survival. There was a strong correlation of survival to tumor size, with 5-year survival rates of 38%, 22%, 5% and 0% in tumors with diameters of ≤2, 2-3, 3-4 and >4 cm respectively. Only 5/20 complete responders had a local recurrence, the 5-year survival in this group was 42%. Patients over 70 years of age with resectable lung cancer, RT with curative intent should be offered as an alternative to operation, especially if the tumor is not >4 cm.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
7. Rosenthal SA, Curran WJ, Jr., Herbert SH, et al. Clinical stage II non-small cell lung cancer treated with radiation therapy alone. The significance of clinically staged ipsilateral hilar adenopathy (N1 disease). *Cancer* 1992; 70(10):2410-2417.	3a	758 total patient records reviewed: 62 patients with stage II NSCLC; 126 patients with N1 disease	To determine the significance of patients with clinically staged hilar nodal involvement (stage N1) or clinical stage II NSCLC (stage T1-2N1M0) treated with RT alone.	The MST of the 62 patients with clinical stage II disease was 17.9 months, with 1-year, 2-year, 3-year, and 5-year overall actuarial survival rates of 70%, 33%, 20%, and 12%, respectively. The survival of patients with clinical stage II disease was significantly better than that of 389 patients with clinical stage IIIA disease (MST, 11.3 months; P<0.008) and 267 patients with clinical stage IIIB disease (MST, 9.8 months; P=0.0003), but it was similar to that of 40 patients with clinical stage I lesions (MST, 15.0 months). Patients with PS of 0-1 lived longer than those with a status of 2 or more (MST, 22.8 vs 6.1 months; P<0.0001). The median survival for patients with N0, N1, N2, and N3 disease was 13.7, 12.6, 10.9, and 9.1 months, respectively. Patients with stage N0-1 disease (MST, 13.2 months) had significantly improved MST compared with those with stage N2-3 disease (MST, 10.3 months). The survival of patients with clinical stage II NSCLC treated with RT alone was significantly better than that of those with clinical stage IIIA or IIIB disease. It was comparable to that of patients with clinical stage I lesions. The clinical staging of nodal involvement limited to the ipsilateral hilum does not necessarily portend a worse prognosis than that of patients with clinical stage N0 disease. The absence of clinically evident stage N2-3 disease is of significant predictive value for patients with NSCLC treated with RT.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
8. Sandler HM, Curran WJ, Jr., Turrisi AT, 3rd. The influence of tumor size and pre-treatment staging on outcome following radiation therapy alone for stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1990; 19(1):9-13.	3a	77 patients	To evaluate the influence of tumor size and pretreatment staging on outcome following RT alone for stage I NSCLC.	The actuarial 3-year survival rate of the entire group of patients is 17% with a MST of 20 months. Of the 61 deaths, 51 were due to disease and 10 were due to intercurrent disease without evidence of tumor recurrence. The actuarial 3-year disease-specific survival was 22%. The 3-year disease-specific survival for patients with tumors <3 cm and from 3-6 cm was 30% and 17%, respectively. Local progression occurred in 33 patients, resulting in a 44%, 3-year actuarial freedom from local progression. The median time to local failure was 28 months and there were no local failures after 3 years in the 18 patients eligible for observation beyond this point. Of the patients with "excellent" staging, only 2/12 were dead of disease compared with 22/24 with "good" staging and 30/41 of the remainder. In this large group of stage I NSCLC, thorough pretreatment staging and smaller tumor size are associated with a more favorable outcome.	2
9. Zhang HX, Yin WB, Zhang LJ, et al. Curative radiotherapy of early operable non-small cell lung cancer. *Radiother Oncol* 1989; 14(2):89-94.	4	44 patients	To retrospectively review patients with early operable NSCLC.	The 1-, 3-, and 5-year survival rates, 93%, 55%, and 32%, are superior to what is reported in the literature. In the present series, the favorable factors are: (1) patients without any intercurrent disease but refused operation, (2) T1 lesions, (3) complete regression of the lesion at the conclusion of RT, and (4) doses ranging from 69 to 70 Gy. It is shown that early NSCLC can be cured by RT alone giving survival rates comparable to surgery. Prospective randomized clinical trials are warranted.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
10. Hayakawa K, Mitsuhashi N, Nakajima N, et al. Radiation therapy for Stage I–III epidermoid carcinoma of the lung. *Lung Cancer* 1992; 8(3-4):213-223.	3a	142 patients	To evaluate patients treated with RT for stage I-III epidermoid carcinoma of the lung.	Patients with PS 0-1 had an actuarial survival of 47% and 24% at 2- and 5-years, compared with 27% and 7% in those with PS 2, and 10% in PS 3 ($y < 0.01$). The actuarial survival rates for stage I, II, IIIA and IIIB were 75%, 44%, 32% and 19% at 2 years, and 31%, 22%, 13% and 10% at 5 years, respectively ($P<0.05$). At 5 years, 26% of the patients with tumors <5 cm in diameter had survived, in contrast to 11% in those with tumors >5 cm in diameter ($P<0.001$). Patients given a total dose of 80 Gy or over had a lower long-term survival rate than those given a total dose of 60-79 Gy. The patients with epidermoid carcinoma of the lung without distant metastasis or malignant effusion were expected to be offered a realistic probability of long-term survival by RT alone.	2
11. McGarry RC, Papiez L, Williams M, Whitford T, Timmerman RD. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. Int J Radiat Oncol Biol Phys 2005; 63(4):1010-1015.	3a	47 patients	Phase I study to assess toxicity and local control rates for patients with medically inoperable stage I lung cancer.	The MTD was not achieved in the T1 stratum (maximum dose = 60 Gy), but within the T2 stratum, the MTD was realized at 72 Gy for tumors >5 cm. Dose-limiting toxicity included predominantly bronchitis, pericardial effusion, hypoxia, and pneumonitis. Local failure occurred in 4/19 T1 and 6/28 T2 patients. Nine local failures occurred at doses < or =16 Gy and only 1 at higher doses. Local failures occurred between 3 and 31 months from treatment. Within the T1 group, 5 patients had distant or regional recurrence as an isolated event, whereas 3 patients had both distant and regional recurrence. Within the T2 group, 2 patients had solitary regional recurrences, and the 4 patients who failed distantly also failed regionally. SBRT seems to be a safe, effective means of treating early-stage lung cancer in medically inoperable patients. Excellent local control was achieved at higher dose cohorts with apparent dose-limiting toxicities in patients with larger tumors.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
12. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004; 101(7):1623-1631.	3a	245 patients	Retrospective evaluation of stereotactic hypofractionated high-dose irradiation for stage I NSCLC.	Hypofractionated high-dose stereotactic irradiation with biologic effective dose <150 Gy was good for curative treatment of patients with stage I NSCLC. Local control and survival rates were better with biologic effective dose ≥100 Gy compared with <100 Gy. Survival rates in medically operable, biologic effective dose ≥100 Gy were excellent.	2
13. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007; 2(7 Suppl 3):S94-100.	3a	257 patients	To retrospectively analyze the treatment outcome of hypofractionated stereotactic RT for stage I NSCLC treated in a Japanese multi-institutional study.	During follow-up (median, 38 months), pulmonary complications of above grade 2 arose in 14 patients (5.4%). Local progression occurred in 36 patients (14.0%), and the local recurrence rate was 8.4% for a biological effective dose of 100 Gy or more compared with 42.9% for <100 Gy (P<0.001). The 5-year OS rate of medically operable patients was 70.8% among those treated with a biological effective dose of 100 Gy or more compared with 30.2% among those treated with less than 100 Gy (P<0.05).	2
14. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010; 303(11):1070-1076.	3a	55 evaluable patients: 44 with T1 tumors; 11 with T2	To evaluate the toxicity and efficacy of SBRT in a high-risk population of patients with early stage but medically inoperable NSCLC.	Median follow-up of 34.4 months (range, 4.8-49.9 months). The estimated 3-year primary tumor control rate was 97.6% (95% CI, 84.3%-99.7%). The rates for DFS 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%). Patients with inoperable NSCLC who received SBRT had a survival rate of 55.8% at 3 years, high rates of local tumor control, and moderate treatment-related morbidity.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
15. 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.	1	452 patients	A randomized phase III trial to compare the following regimens: 1) standard RT, 2) induction chemotherapy followed by standard RT, and 3) twice-daily RT.	Toxicity was acceptable, with 4 treatment-related deaths. 1-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 (logrank P=.03). In "good-risk" patients with surgically unresectable NSCLC, induction chemotherapy followed by RT was superior to hyperfractionated RT or standard RT alone, yielding a statistically significant short-term survival advantage.	1
16. 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.	1	610 patients	To compare concurrent once-daily radiation against 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.	MSTs 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 thoracic RT compared with the sequential treatment (5-year survival: sequential, arm 1, 10% [20 patients], 95% CI = 7% to 15%; concurrent, arm 2, 16% [31 patients], 95% CI = 11% to 22%, P=.046; concurrent, arm 3, 13% [22 patients], 95% CI = 9% to 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

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
17. Pigott KH, Saunders MI. The long-term outcome after radical radiotherapy for advanced localized non-small cell carcinoma of the lung. *Clin Oncol (R Coll Radiol)* 1993; 5(6):350-354.	3a	76 patients	To observe the incidence of locoregional failure, distant metastases and intercurrent disease in patients with advanced localized NSCLC.	Overall median survival for the group was 12.8 months, with patients attaining locoregional control faring better, with a median survival of 27.9 months compared with 9.9 months for those who did not achieve locoregional control. The life-tables show a 52% survival probability at 1 year for the whole group, but those attaining locoregional control showed a 75% survival probability compared with 39% for patients failing to achieve complete regression; these figures fell to 62% and 6% respectively at 2 years. The remaining 58 patients died with locoregional disease, with 35 also showing evidence of distant metastases.	2
18. Slotman BJ, Antonisse IE, Njo KH. Limited field irradiation in early stage (T1-2N0) non-small cell lung cancer. *Radiother Oncol* 1996; 41(1):41-44.	3a	31 patients	To investigate whether limited field irradiation, without irradiation of regional lymph nodes, can safely be used in these patients.	OS was 42% at 3 years. Disease-specific survival at 3 years was 76%. One patient developed an isolated regional failure, one had a combined local and distant failure, and one had a combined local, regional and distant failure, while three patients failed at distant sites only. Thus, only two patients (6%) recurred regionally. This study shows that 'postage stamp' irradiation is an effective alternative to surgery. Radiation of the hilar and mediastinal lymph nodes can be omitted in these pulmonary compromised patients.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
19. Rosenzweig KE, Sura S, Jackson A, Yorke E. Involved-field radiation therapy for inoperable non small-cell lung cancer. *J Clin Oncol* 2007; 25(35):5557-5561.	4	524 patients	To implement the use of IFRT in an effort to reduce toxicity while treating the gross tumor to higher doses. This analysis reports failure rates in uninvolved nodal regions with the use of IFRT.	Only 32 patients (6.1%) with elective nodal failure were identified. The 2-year actuarial rates of elective nodal control and primary tumor control were 92.4% and 51%, respectively, with a median follow-up of 41 months in survivors. In patients who achieved local disease control, the 2-year elective nodal control rate was 91%. The median time to elective nodal failure was 6 months (range, 0 to 56 months). Many patients experienced treatment failure in multiple lymph node regions simultaneously. The use of IFRT did not cause a significant amount of failure in lymph node regions not included in the tumor volume. Therefore, IFRT remains an acceptable method of treatment that allows for dose escalation while minimizing toxicity.	2
20. 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.	1	200 patients	A randomized study of IFRT vs elective nodal RT in combination with concurrent chemotherapy in patients with 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% vs36%, P=0.032) than those in the elective nodal RT arm. The radiation pneumonitis rate in patients with IFRT was lower than in patients with elective nodal RT (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 RT 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

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
21. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 1999; 45(2):323-329.	4	99 patients	To identify a clinically relevant and available parameter upon which to identify NSCLC patients at risk for pneumonitis when treated with 3D RT.	Univariate analysis revealed the percent of the total lung volume exceeding 20 Gy (V20), the effective volume and the total lung volume mean dose, and location of the tumor primary (upper vs lower lobes) to be statistically significant relative to the development of ≥Grade 2 pneumonitis. Multivariate analysis revealed the V20 to be the single independent predictor of pneumonitis. The V20 from the total lung dose-volume histograms is a useful parameter easily obtained from most 3D treatment planning systems. The V20 may be useful in comparing competing treatment plans to evaluate the risk of pneumonitis for our individual patient treatment and may also be a useful parameter upon which to stratify patients or prospective dose escalation trials.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
22. Marks LB, Munley MT, Bentel GC, et al. Physical and biological predictors of changes in whole-lung function following thoracic irradiation. *Int J Radiat Oncol Biol Phys* 1997; 39(3):563-570.	3a	100 patients	To develop methods of predicting the pulmonary consequences of thoracic RT by prospectively studying changes in pulmonary function following RT.	RT-induced symptoms developed in 21 patients. In the overall group, the single best predictor for the development of symptoms was the normal tissue complication probability (P<0.05). Pre-RT pulmonary function tests alone were less predictive (P=0.1 for forced expiratory volume1, P=0.08 for diffusion capacity). A multivariate model based on pre-RT diffusion capacity and CT-based normal tissue complication probability was strongly predictive for the development of symptoms (P<0.001). Normal tissue complication probability based on SPECT-derived functional dose-volume histograms and serial transforming growth factor-beta -beta1 levels did not appear to provide additional predictive value. The presence or absence of pulmonary symptoms was correlated with the decline in pulmonary function test 6 months following RT (P<0.05). In the overall group, the degree of decline in pulmonary function tests was not well correlated with any of the dose-volume variables considered. In patients with "good" pre-RT pulmonary function tests, there was a relationship between the percent reduction in pulmonary function test and dose-volume parameters such as the percent of lung volume receiving >30 Gy (P<0.05). The extent of alteration in whole-lung function (symptoms or pulmonary function test changes) appears to be related to both dose-volume and pre-RT pulmonary function test parameters. The data suggest that no one variable is likely to be an adequate predictor and that multivariate predictive models will be needed.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
23. Martel MK, Ten Haken RK, Hazuka MB, Turrisi AT, Fraass BA, Lichter AS. Dose-volume histogram and 3-D treatment planning evaluation of patients with pneumonitis. *Int J Radiat Oncol Biol Phys* 1994; 28(3):575-581.	3a	63 total patients: 21 with Hodgkin's disease; 42 with NSCLC	Retrospective study to analyze 3-D dose distributions and dose-volume histograms for patients who have had normal lung irradiated in two types of treatment situations.	5 Hodgkin's disease patients and 9 lung cancer patients developed pneumonitis. Comparisons of averages of mean lung dose and normal tissue complication probabilities show a difference between patients with and without complications. Averages of calculated normal tissue complication probabilities for groups of patients show that empirical model parameters correlate with actual complication rates for the Hodgkin's patients, but not as well for the individual lungs of the lung cancer patients treated to larger volumes of normal lung and high doses. This study gives useful data for the characterization of the dose-volume relationship and the development of pneumonitis. These data can be used to help set up a dose escalation protocol for the treatment of NSCLC.	2

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24. Graham MV, Purdy JA, Harms W, Bosch W, Wasserman TH, Perez CA. Survival and prognostic factors of non-small cell lung cancer (NSCLC) patients treated with definitive three-dimensional (3D) radiation therapy. *Int J Radiat Oncol Biol Phys* 1998; 42(suppl 1):166.	3a	100 total patients: 21 stage I; 6 stage II; 49 stage IIIA; 24 stage IIIB	To identify prognostic factors and survival in NSCLC patients treated with definitive 3D RT.	Median, 1, 2, and 3 year survivals for the entire group were 13.8 months, 57% and 46% and 39%, respectively. Cause specific survival was strongly predicted by the gross tumor volume (P<0001). OS did not correlate with clinical stage (P=.65). OS was most correlated with % volume exceeding 20 Gy (P<.001) (persons with higher lung volumes treated had poorer survival secondary to complications including death), age (P=.003) (younger patients survived longer) and the gross tumor volume (cc) P=.005 (smaller tumors survived longer). For tumors with gross tumor volume less than 70 cc the OS was significantly greater in patients receiving higher radiation tumor dose (mean dose >74 Gy and/or maximum dose >79 Gy). No dose effect could be seen for tumors with GTV >70 cc. This data suggests that certain parameters derived from 3D RTP can be useful to predict outcomes of definitive RT and may be stronger prognostic factors than the traditional ones used for surgical treatment. This data also points out the importance of quality RT and radiation dose for optimal survival. Cooperative group prospective clinical trials with 3D radiation treatment planning and the development of a relevant database are needed to further identify and clarify the most important prognostic factors specific to RT.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
25. Robertson JM, Ten Haken RK, Hazuka MB, et al. Dose escalation for non-small cell lung cancer using conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 1997; 37(5):1079-1085.	4	48 patients	To design a RT dose escalation trial, where the dose is determined by (a) the effective volume of normal lung irradiated, and (b) the estimated risk of a complication.	Current doses in the 5 treatment bins are 69.3, 69.3, 75.6, 84, and 92.4 Gy. None of the 15 evaluable patients in any bin with ≥30% normal tissue complication probability experienced clinical radiation pneumonitis, implying that the actual risk is <20% (beta error rate 5%). Despite the observation of the clinically negative lymph nodes at high risk, there has been no failure in the untreated mediastinum as the sole site of first failure. 3/10 patients receiving ≥84 Gy have had biopsy proven residual or locally recurrent disease. Successful dose escalation in a volume-dependent organ can be performed using this technique. By incorporating the effective volume of irradiated tissue, some patients have been treated to a total dose of radiation over 50% higher than traditional doses. The literature-derived parameters appear to overestimate pneumonitis risk with higher volumes. There has been no obvious negative effect due to exclusion of elective lymph node radiation. When completed, this trial will have determined the maximum tolerable dose of RT as a single agent for NSCLC and the appropriate dose for Phase II investigation.	2

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26. Martel MK, Ten Haken RK, Hazuka MB, et al. Estimation of tumor control probability model parameters from 3-D dose distributions of non-small cell lung cancer patients. *Lung Cancer* 1999; 24(1):31-37.	4	76 patient treatment plans	To derive D50 and gamma from clinical experience using 3-D treatment planning to treat NSCLC patients.	Tumor volumes ranged from 4.3 to 856 cc. Calculated volumes in the study were compared to the volumes for a 3-, 4-, 5- and 6-cm diameter sphere. There were 4 tumors with volumes <14 cc (3 cm diameter), 8 tumor volumes <33.5 cc (4 cm diameter), 15 tumor volumes <65.5 cc (5 cm diameter) and 27 tumor volumes<113 cc (6 cm diameter). The remainder of the 49 patients had tumor volumes >113 cc. The results of this study suggest that for NSCLC patients, the dose to achieve significant probability of tumor control (~50%) may be large (on the order of 84 Gy) to achieve longer (~30 months) local PFS. Doses on the order of 84 Gy (corrected) and higher have been given conformally to the tumor volume in the current NSCLC dose escalation protocol. Thus far, deliverance of high doses has been clinically achievable without causing unacceptable normal tissue toxicity.	2
27. Armstrong JG, Burman C, Leibel S, et al. Three-dimensional conformal radiation therapy may improve the therapeutic ratio of high dose radiation therapy for lung cancer. *Int J Radiat Oncol Biol Phys* 1993; 26(4):685-689.	5	9 patients	To evaluate the feasibility of tumor dose escalation for patients with lung cancer, by determining the dose distribution to the target and normal tissues with 3D-CRT and conventional planning.	The mean percentage of gross disease which received ≤70.2 Gy with 3D-CRT was 40% of the mean percentage of gross disease which received ≤70.2 Gy with conventional treatment planning. The mean normal tissue complication probabilities for lung parenchyma with 3D-CRT were 36% of the mean normal tissue complication probabilities with conventional treatment planning. The mean esophageal normal tissue complication probabilities with 3D-CRT were 88% of the mean normal tissue complication probabilities with conventional treatment planning. This preliminary analysis suggests that 3D-CRT may provide superior delivery of high dose radiation with reduced risk to normal tissue, suggesting that this approach may have the potential to improve the therapeutic ratio of high dose RT for lung cancer.	4

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28. Hayman JA, Martel MK, Ten Haken RK, et al. Dose escalation in non-small-cell lung cancer using three-dimensional conformal radiation therapy: update of a phase I trial. *J Clin Oncol* 2001; 19(1):127-136.	4	104 total patients: 24 stage I; 4 stage II; 43 stage IIIA; 26 stage IIIB; 7 locally recurrent disease	Phase I study to determine whether high-dose radiation may improve outcomes in NSCLC.	The maximum-tolerated dose was only established for the largest bin, at 65.1 Gy. Dose levels for the four remaining bins were 102.9, 102.9, 84 and 75.6 Gy. The majority of patients failed distantly, though a significant proportion also failed in the target volume. There were no isolated failures in clinically uninvolved nodal regions. Dose escalation in NSCLC has been accomplished safely in most patients using 3D-CRT, limiting target volumes, and segregating patients by the volume of normal lung irradiated.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
29. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2005; 61(2):318-328.	1	177 patients	Randomized trial to evaluate prospectively the acute and late morbidities from a multi-institutional 3D RT dose-escalation study for inoperable NSCLC.	The following acute Grade 3 or worse toxicities were observed for Group 1: 70.9 Gy (1 case of weight loss), 77.4 Gy (nausea and hematologic toxicity in 1 case each), 83.8 Gy (1 case of hematologic toxicity), and 90.3 Gy (3 cases of lung toxicity). The following acute Grade 3 or worse toxicities were observed for Group 2: none at 70.9 Gy and 2 cases of lung toxicity at 77.4 Gy. The estimated rate of Grade 3 or worse late lung toxicity at 18 months was 7%, 16%, 0%, and 13% for Group 1 patients receiving 70.9, 77.4, 83.8, or 90.3 Gy, respectively. Group 2 patients had an estimated late lung toxicity rate of 15% at 18 months for both 70.9 and 77.4 Gy. The prognostic factors for late pneumonitis in multivariate analysis were the mean lung dose and V(20). The estimated rate of late Grade 3 or worse esophageal toxicity at 18 months was 8%, 0%, 4%, and 6%, for Group 1 patients receiving 70.9, 77.4, 83.8, 90.3 Gy, respectively, and 0% and 5%, respectively, for Group 2 patients receiving 70.9 and 77.4 Gy. The observed locoregional control and OS rates were each similar among the study arms within each dose level of Groups 1 and 2. Locoregional control was achieved in 50%-78% of patients. The radiation dose was safely escalated using 3D-CRT to 83.8 Gy for patients with V(20) values of <25% (Group 1) and to 77.4 Gy for patients with V(20) values between 25% and 36% (Group 2), using fraction sizes of 2.15 Gy. The 90.3-Gy dose level was too toxic, resulting in dose-related deaths in 2 patients. Elective nodal failure occurred in <10% of patients.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
30. Rosenzweig KE, Fox JL, Yorke E, et al. Results of a phase I dose-escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable nonsmall cell lung carcinoma. *Cancer* 2005; 103(10):2118-2127.	4	104 patients	To report the results of a Phase I dose-escalation study using 3D-CRT for the treatment of patients with NSCLC.	Unacceptable pulmonary toxicity occurred at 90.0 Gy. Subsequently, another 10 patients were accrued at the 84.0 Gy level with acceptable toxicity. Thus, 84.0 Gy was the MTD. The crude late pulmonary toxicity rate was 7%, the 2-year local control rate was 52%, the DFS rate was 33%, and the OS rate was 40%. The median survival was 21.1 months. OS was improved significantly in patients who received ≥80.0 Gy. The MTD of 3D-CRT for NSCLC with normal tissue complication probabilities constraint of 25% was 84.0 Gy in the current study. There was a suggestion of improved survival in patients who received 80.0 Gy.	2
31. 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.	3c	68 patients treated with IMRT; 222 patients had 3D-CRT	Retrospective study to examine the rate of high-grade treatment-related pneumonitis in patients with advanced NSCLC treated with concurrent chemotherapy and IMRT.	Despite the IMRT group's larger gross tumor volume, the rate of grade ≥3 treatment-related pneumonitis at 12 months was 8% compared with 32% for 3D-CRT (P=0.002). Study concludes that in advanced NSCLC patients treated with chemoradiation, IMRT resulted in significantly lower levels of grade ≥3 treatment-related pneumonitis compared with 3D-CRT.	2
32. Chang JY, Komaki R, Wen HY, et al. Toxicity and patterns of failure of adaptive/ablative proton therapy for early-stage, medically inoperable non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; 80(5):1350-1357.	3a	18 patients	To analyze the toxicity and patterns of failure of proton therapy given in ablative doses for medically inoperable early-stage NSCLC.	At a median follow-up time of 16.3 months (range, 4.8-36.3 months), no patient had experienced Grade 4 or 5 toxicity. The most common adverse effect was dermatitis (Grade 2, 67%; Grade 3, 17%), followed by Grade 2 fatigue (44%), Grade 2 pneumonitis (11%), Grade 2 esophagitis (6%), and Grade 2 chest wall pain (6%). Rates of local control were 88.9%, regional lymph node failure 11.1%, and distant metastasis 27.8%. Twelve patients (67%) were still alive at the last follow-up; five had died of metastatic disease and one of preexisting cardiac disease. Proton therapy to ablative doses is well tolerated and produces promising local control rates for medically inoperable early-stage NSCLC.	3

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
33. 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.	3a	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.	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. Nineteen (43.2%) patients developed distant metastasis. The OS and PFS rates were 86% and 63% at 1 year.	2
34. Sejpal S, Komaki R, Tsao A, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer. *Cancer* 2011; 117(13):3004-3013.	3a	62 patients	Study hypothesized that proton beam therapy for most patients with NSCLC could permit higher tumor doses with less normal-tissue toxicity than photon RT delivered as 3D-CRT or IMRT.	Median follow-up times were 15.2 months (proton), 17.9 months (3D-CRT), and 17.4 months (IMRT). Median total radiation dose was 74 Gy (RBE) for the proton group vs 63 Gy for the other groups. Rates of severe (grade ≥ 3) pneumonitis and esophagitis in the proton group (2% and 5%) were lower despite the higher radiation dose (3D-CRT, 30% and 18%; IMRT, 9% and 44%; P<.001 for all).	3
35. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* 1990; 323(14):940-945.	1	155 total patients: Group 1 - 78 patients; Group 2 -77 patients	Randomized trial to determine whether induction chemotherapy before irradiation improves survival.	The median survival was greater for those in group 1 — 13.8 vs 9.7 months (P=0.0066 by log-rank test). Rates of survival in group 1 were 55% after 1 year, 26% after 2 years, and 23% after 3 years, as compared with 40%, 13%, and 11%, respectively, in group 2. Those in group 1 had a higher incidence of serious infections requiring hospitalization (7%, vs 3% in group 2) and severe weight loss (14% vs 6%), but there were no treatment-related deaths. In patients with stage III NSCLC, induction chemotherapy with cisplatin and vinblastine before radiation significantly improves median survival (by about 4 months) and doubles the number of long-term survivors, as compared with RT alone. Since three-quarters of the patients still die within 3 years, however, further improvements in systemic and local therapy are needed.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
36. 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.	1	353 (177 had RT alone and 176 had combined treatment)	Randomized study comparing RT alone to combined RT and chemotherapy in unresectable squamous cell and large cell lung carcinoma.	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
37. Mattson K, Holsti LR, Holsti P, et al. Inoperable non-small cell lung cancer: radiation with or without chemotherapy. *Eur J Cancer Clin Oncol* 1988; 24(3):477-482.	1	238 patients	Randomized, multicentre study of split-course RT, with or without combination chemotherapy in patients with inoperable NSCLC.	No significant difference was apparent between the RT and the RT-chemotherapy arms with respect to objective response rates (complete response + partial response) (44% and 49%, respectively), median duration of response (278 and 320 days), local failure (31% and 20%), distant progression (23% and 20%) or median survival (311 and 322 days). The survival figures showed an almost significant (P=0.05) therapeutic advantage of the combined regimen with stage IIIM0 disease. Progressive disease was the cause of death in 92% and 88%. Chemotherapy did not contribute significantly to either local control or survival as compared to RT alone.	1
38. Trovo MG, Zanelli GD, Minatel E, Franchin G, Gobitti C. Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1992; 24(3):573-574. (11-15)	1	173 patients	Randomized trial to compare RT only (45 Gy/15 fractions/3 weeks) (arm A) vs RT and a daily low dose of cisplatin (6 mg/m^2) (arm B).	No differences in the pattern of relapse were noted between the two treatment groups. Median time to progression was 10.6 months for arm A and 14.2 months for arm B. Median survivals were 10.3 months and 9.97 months, respectively. Toxicity was acceptable and no treatment-related death occurred in either treatment schedule. In this study no significant advantage of the combined treatment over RT only was found. The encouraging results achieved in some trials together with the intractability of the disease suggest that further efforts should be made to optimize clinical trial protocols, perhaps by reviewing the radiobiological and pharmacological basis of the combined treatment.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
39. Wolf M, Hans K, Becker H, et al. Radiotherapy alone versus chemotherapy with ifosfamide/vindesine followed by radiotherapy in unresectable locally advanced non-small cell lung cancer. *Semin Oncol* 1994; 21(3 Suppl 4):42-47.	1	85 patients	Randomized, multicenter study to compare RT alone vs chemotherapy with ifosfamide/vindesine followed by RT in unresectable locally advanced NSCLC.	Of the patients receiving chemotherapy, 25% had a partial remission after 2-cycles, 46% showed no change, and 29% had progressive disease. After RT, response rates were 49% in Arm A and 58% in Arm B, including a 10% complete remission rate in both groups. Median survival was 9 months vs 13.7 months and 2-year survival was 12% vs 24%, both in favor of the group receiving chemotherapy. Results indicate that chemotherapy is able to prolong survival.	1
40. 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.	1	155 patients (78 randomly assigned to the CT-RT group and 77 randomly assigned to the RT group)	Present long-term survival results based on a median follow-up of more than 8 years for patients enrolled in CALGB 8433 trial. A randomized trial of induction chemotherapy plus high dose radiation vs radiation alone in stage III NSCLC.	Rate of tumor response 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 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% for the chemotherapy-RT group and 40%, 13%, 10%, 7%, 6%, 6%, and 6% for the RT group. Long-term follow-up confirms that patients with stage III NSCLC who receive 5 weeks of chemotherapy with cisplatin and vinblastine before RT have a 4.1-month increase in median survival.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
41. Atagi S, Kawahara M, Yokoyama A, et al. Thoracic radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301). *Lancet Oncol* 2012; 13(7):671-678.	1	200 patients; 100 in chemoradiotherapy group and 100 in RT group	Randomized phase 3 trial to assess whether RT plus carboplatin results in longer survival than RT alone in elderly patients with NSCLC.	Median OS for the chemoradiotherapy and RT alone groups were 22.4 months (95% CI 16.5-33.6) and 16.9 months (13.4-20.3), respectively (HR = 0.68, 95.4% CI 0.47-0.98, stratified log-rank test one-sided P=0.0179). More patients had grade 3-4 haematological toxic effects in the chemoradiotherapy group than in the RT alone group, including leucopenia (61 [63.5%] vs none), neutropenia (55 [57.3%] vs none), and thrombocytopenia (28 [29.2%] vs 2 [2.0%]). Grade 3 infection was more common with chemoradiotherapy (12 patients [12.5%]) than with RT (4 patients [4.1%]). Incidences of grade 3-4 pneumonitis and late lung toxicity were similar between groups. There were 7 treatment-related deaths: 3/100 patients (3.0%) in the chemoradiotherapy group and 4/100 (4.0%) in the RT group.	1
42. 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.	4	63 patients	To evaluate the addition of gefitinib to sequential or concurrent chemoradiotherapy in unresectable stage III NSCLC.	Acute high-grade infield toxicities were not clearly increased compared with historical chemoradiotherapy 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 EGFR mutations and 2 of 13 also had T790M mutations. Seven tumors of 45 had KRAS mutations. There was no apparent survival difference with EGFR-activating mutations vs wild type or KRAS mutation vs wild type. Survival of poor-risk patients with wild type or mutated EGFR receiving sequential chemoradiotherapy with gefitinib was promising. Survival for good-risk patients receiving concurrent chemoradiotherapy plus gefitinib was disappointing even for tumors with activating EGFR mutations.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
43. Jensen AD, Munter MW, Bischoff HG, et al. Combined treatment of nonsmall cell lung cancer NSCLC stage III with intensity-modulated radiotherapy and cetuximab: the NEAR trial. *Cancer* 2011; 117(13):2986-2994.	3a	30 patients	To evaluate efficacy and toxicity of radioimmunotherapy with IMRT and cetuximab in stage III NSCLC.	Overall response rate was 63% (partial remission: 19/30) patients. Median locoregional, distant, overall PFS was 20.5, 10.9, and 8.5 months. Median OS was 19.5 months, with an estimated 1- and 2-year survival of 66.7% and 34.9% respectively. Stage (IIIA vs IIIB) and histologic subtype did not have a significant impact on survival rates in patients. Treatment was tolerated well with only mild toxicity (degrees 3 pneumonitis: 3.3%, any degrees 3 acute toxicity: 36.7%).	2
44. Jatoi A, Schild SE, Foster N, et al. A phase II study of cetuximab and radiation in elderly and/or poor performance status patients with locally advanced non-small-cell lung cancer (N0422). *Ann Oncol* 2010; 21(10):2040-2044.	3a	57 patients	The authors tested cetuximab + radiation in elderly and/or poor PS patients with locally advanced NSCLC to determine a tolerable but effective regimen.	40/57 (70%) lived 11+ months, thus exceeding the anticipated survival rate of 50%. The median survival was 15.1 months [95% CI 13.1-19.3 months], and the median time to cancer progression was 7.2 months (95% CI 5.8-8.6 months). No treatment-related deaths occurred, but 31 patients experienced grade 3+ adverse events, most commonly fatigue, anorexia, dyspnea, rash, and dysphagia, each of which occurred in <10% of patients.	2
45. Gore E, Bae K, Langer C, et al. Phase I/II trial of a COX-2 inhibitor with limited field radiation for intermediate prognosis patients who have locally advanced non-small-cell lung cancer: radiation therapy oncology group 0213. *Clin Lung Cancer* 2011; 12(2):125-130.	3a	Phase 1: 8 patients; Phase 2: 5 patients	To test a low toxicity treatment regimen in the treatment of patients who have locally advanced NSCLC and compromised PS or weight loss.	The phase I component accrued 8 patients each at 200 mg twice daily and 400 mg twice daily. Twice daily 400 mg was chosen for the phase II component, which enrolled 5 patients and was closed early because of poor accrual. We were able to analyze 18 patients. PS ratings were 0, 1, and 2 in 7, 7, and 4 patients, respectively. Median age was 72 years. Weight loss of greater than 5% was noted in 10 patients (56%). Four of 10 had weight loss ≥20%. Median follow-up and survival was 10 months. OS rates at 1 and 2 years were 44.4% [95% CI, 21.6%-65.1%] and 22.2% (95% CI, 6.9%-42.9%), respectively. PFS at 1 year was 33.3% (95% CI, 13.7%-54.5%). Toxicities matched those expected with thoracic RT alone. Concurrent thoracic RT and celecoxib was well tolerated. The sample size was too small to draw conclusions regarding efficacy.	4

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
46. 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 4 January 2012.	1	544 patients	To compare the OS of patients treated with high-dose vs standard-dose conformal RT in the setting of concurrent chemotherapy and to compare the OS of patients treated with cetuximab vs without cetuximab in the setting of concurrent chemotherapy.	Results of an early analysis of study data (scheduled to take place upon 90 participant deaths being reported) demonstrated that the higher dose of radiation did not improve OS, at which time the two high-dose RT arms were closed to further participant enrollment. Based on this trial result, the standard dose of RT for stage III NSCLC remains at 60 Gy. It was also reported that there was no significant difference in treatment-related toxicity between the high-dose and standard radiation treatment arms. Study participants continue to be enrolled in the two arms of the RTOG 0617 trial evaluating standard-dose RT administered at the same time as chemotherapy with or without the drug cetuximab.	3
47. Kubota K, Furuse K, Kawahara M, et al. Role of radiotherapy in combined modality treatment of locally advanced non-small-cell lung cancer. *J Clin Oncol* 1994; 12(8):1547-1552.	1	92 patients	Randomized trial using cisplatin -based chemotherapy regimens with or without thoracic RT.	63 patients were included in the second randomization. The patients in the chemotherapy/RT group (n=32) and chemotherapy-alone group (n=31) were comparable in terms of age, sex, PS, histologic features, stage of disease, and induction chemotherapy regimen. The median durations of survival were similar for the two groups (461 days in chemotherapy/RT group and 447 days in chemotherapy-alone group). The survival rate in the chemotherapy/RT group was 58% at 1 year, 36% at 2 years, and 29% at 3 years, as compared with 66%, 9%, and 3% at 1, 2, and 3 years, respectively, in the chemotherapy-alone group. One patient in the chemotherapy/RT group died of pneumonitis, but there were no chemotherapy-related deaths. In locally advanced NSCLC, P-based combination chemotherapy followed by chest irradiation significantly increases the number of long-term survivors as compared with chemotherapy alone. RT to bulky disease in the thorax is thus an important part of combined modality therapy, and a necessary part of further studies in locally advanced disease.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
48. Rodrigues G, Videtic GMM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. *Practical Radiation Oncology* 2011; 1(2):60-71.	15	3 systematic reviews (14 randomized control trials, 6 randomized control trials, 8 prospective studies)	To provide guidance to physicians and patients with regard to the use of EBRT, endobronchial brachytherapy, and concurrent chemotherapy in the setting of palliative thoracic treatment for lung cancer, based on available evidence complemented by expert opinion.	Studies suggest that higher dose/fractionation palliative EBRT regimens (eg, 30 Gy/10 fraction equivalent or greater) are associated with modest improvements in survival and total symptom score, particularly in patients with good PS.	4
49. Simpson JR, Francis ME, Perez-Tamayo R, Marks RD, Rao DV. Palliative radiotherapy for inoperable carcinoma of the lung: final report of a RTOG multi-institutional trial. *Int J Radiat Oncol Biol Phys* 1985; 11(4):751-758.	1	316 total evaluable patients	RTOG randomized prospective total for palliation of symptoms-NSCLC 40 Gy split course vs 30 Gy vs 40 Gy.	Palliation of symptoms was achieved in 60% with one-fourth of the patients becoming symptom-free. Complete regression of local and regional tumor was produced in 15% and partial regression in 26%. There is no significant difference between the treatment arms in these objective response rates. MST was approximately 6 months. No significant benefit was demonstrated by the adjuvant use of Cytoxan. Although the number of complete responses produced was relatively small, patients achieving a complete response had a significantly longer median survival than the remaining patients, (ie, 14.5 months vs 6 months). Significant toxicity occurred in fewer than 6% of patients. Radiation pneumonitis counted for the majority of these adverse reactions. Toxicity occurred somewhat more often in the group treated with 40 Gy split course therapy.	1
50. Macbeth FR, Bolger JJ, Hopwood P, et al. Randomized trial of palliative two-fraction versus more intensive 13-fraction radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Medical Research Council Lung Cancer Working Party. *Clin Oncol (R Coll Radiol)* 1996; 8(3):167-175.	1	509 total patients from 11 centers	Prospective randomized trial with stage IV NSCLC patients to compare outcomes of 17 Gy in 2 fractions vs 39 Gy in 13 fractions for palliative treatment.	17 Gy in 2 fractions gave a more rapid relief of symptoms but 39 Gy in 13 fractions gave a longer MST (9months vs 7 months). Higher total dose was correlated to increased survival time.	1
51. Bezjak A, Dixon P, Brundage M, et al. Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer (NCIC CTG SC.15). *Int J Radiat Oncol Biol Phys* 2002; 54(3):719-728.	1	231 total patients	Prospective randomized phase III trial in patients with advanced NSCLC to compare outcomes of 20 Gy in 5 fractions vs 10 Gy in a single fraction for palliative treatment.	Similar palliation was seen in both arms but the 20 Gy in 5 fractions had an increased median survival (6 months vs 4.2 months). Higher total dose was correlated to increased survival time.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
52. Pirtoli L, Bindi M, Bellezza A, Pepi F, Tucci E. Unfavorable experience with hypofractionated radiotherapy in unresectable lung cancer. *Tumori* 1992; 78(5):305-310.	4	86 patients	To report experience with hypofractionated RT for palliation of stage III-IV NSCLC.	Subjective and PS improvement, and survival overall were as poor as could be expected in this kind of presentation, with no striking impact of this treatment modality. Severe adverse effects were shown by a large proportion of cases involving skin and soft tissues of the chest wall (40%) and lungs (55.5%). The incidence of severe damage was in agreement with biologic effective dose values, differently from other experiences of radiotherapeutic management of advanced lung cancer with large fractions.	2
53. Inoperable non-small-cell lung cancer (NSCLC): a Medical Research Council randomised trial of palliative radiotherapy with two fractions or ten fractions. Report to the Medical Research Council by its Lung Cancer Working Party. *Br J Cancer* 1991; 63(2):265-270.	1	369 total patients	Randomized study to compare two policies of palliative thoracic RT for NSCLC.	Palliation of the main symptoms was achieved in high proportions of patients ranging in the F2 group from 65% for cough to 81% for haemoptysis and in the FM group from 56% for cough to 86% for haemoptysis. Haemoptysis, chest pain, and anorexia disappeared for a time in well over half the patients with these symptoms, and cough in 37%. For all the main symptoms, the median duration of palliation was 50% or more of survival. PS improved in approximately half of the patients with a poor status on admission. All these results were similar in the two treatment groups. As assessed daily by the patients using a diary card, the QOL deteriorated slightly during treatment but then improved steadily during the next 5 weeks. The proportion of patients with dysphagia increased considerably during treatment, but fell to the pretreatment level during the next 2 weeks. The results were similar in the two groups. Radiation myelopathy was suspected in one (F2) patient. There was no difference in survival between the two groups (log-rank test), the MST from the date of allocation being 179 days in the F2 and 177 days in the FM group. In the light of all the findings, the regimen of two fractions of 8.5 Gy given 1 week apart is recommended.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
54. Collins TM, Ash DV, Close HJ, Thorogood J. An evaluation of the palliative role of radiotherapy in inoperable carcinoma of the bronchus. *Clin Radiol* 1988; 39(3):284-286.	3a	96 patients	To evaluate the palliative role of RT in patients with inoperable carcinoma of the bronchus.	The median survival of the group as a whole was 38 weeks. Major symptoms such as cough, dyspnoea and haemoptysis were well controlled at 3 months and 6 months follow-up. There was no significant effect on PS. Dysphagia and tiredness occurred in 81% of patients, but were classed as mild in 41% and 47% respectively, lasting less than 4 weeks in 86%. There was no correlation between the RT dose received and symptom control. 14% of patients were dead within approximately 3 months of treatment and were unlikely to have benefited from therapy. Careful selection of patients for palliative RT is recommended.	2
55. Teo P, Tai TH, Choy D, Tsui KH. A randomized study on palliative radiation therapy for inoperable non small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 1988; 14(5):867-871.	1	291 patients	Randomized two-arm study to evaluate palliative RT for inoperable NSCLC.	Prognosis was poor with an overall median survival of 20 weeks and was similar in both arms. Radiological tumor response was also similar: 53% in arm 1 and 50% in arm 2. However, arm 1 was superior than arm 2 in achieving symptom palliation, 71% vs 54%, ($P<0.02$). Treatment complications were mild and included mainly radiation oesophagitis and pneumonitis and pulmonary fibrosis. Treatments in both arms were equally well tolerated.	1
56. Carroll M, Morgan SA, Yarnold JR, Hill JM, Wright NM. Prospective evaluation of a watch policy in patients with inoperable non-small cell lung cancer. *Eur J Cancer Clin Oncol* 1986; 22(11):1353-1356.	3a	134 patients	To evaluate inoperable NSCLC with immediate vs delayed RT for palliative symptom control.	Median symptom-free survival in this group was 10 months. The requirement for immediate or delayed chest irradiation could not be predicted from either patient or tumor characteristics. The proportion of patients with NSCLC requiring palliative chest irradiation may have been overestimated from this study population; even so 22/134 patients (16%) did not at any stage in their illness require RT for chest symptoms.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
57. Fairchild A, Harris K, Barnes E, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. *J Clin Oncol* 2008; 26(24):4001-4011.	7 (systematic review)	3,473 total patients; 13 randomized control trials	To systematically review randomized trials of palliative thoracic RT.	Outcomes included symptom palliation, OS, toxicity, and reirradiation rate. For symptom control in assessable patients, lower-dose RT was comparable with higher-dose, except for the total symptom score: 65.4% of lower-dose and 77.1% of higher-dose patients had improved total symptom score (P=.003). Greater likelihood of symptom improvement was seen with schedules of 35 Gy(10) vs lower biologically equivalent dose. At 1 year after higher-dose and lower-dose RT, 26.5% vs 21.7% of patients were alive, respectively (P=.002). Sensitivity analysis suggests this survival improvement was seen with 35 Gy(10) biologically equivalent dose schedules compared with lower-doses. Physician-assessed dysphagia was significantly greater in the higher-dose arm (20.5% v 14.9%; P=.01), and the likelihood of reirradiation was 1.2-fold higher after lower-dose RT. No significant differences were observed for specific symptom-control end points, although improvement in survival favored higher-dose RT. Consideration of palliative thoracic RT of at least 35 Gy(10) biologically equivalent dose may therefore be warranted, but must be weighed against increased toxicity and greater time investment.	2
58. Zajac AJ, Kohn ML, Heiser D, Peters JW. High-dose-rate intraluminal brachytherapy in the treatment of endobronchial malignancy. Work in progress. *Radiology* 1993; 187(2):571-575.	4	72 patients	To evaluate high-dose-rate intraluminal brachytherapy in the treatment of endobronchial malignancy.	A substantial reduction, N airway disease and an improvement in symptoms were seen in 82% of patients. Obstruction scores showed an overall 74% improvement. Complications occurred in only 10 patients (two of whom died). Median survival was short (palliative group, 5 months; definitive group, 12 months); however, symptoms remained palliated in 62 patients (76%) until death or the last follow-up examination. Remote afterloading high-dose-rate brachytherapy is effective and can be applied with equal success in all patients with malignant airway obstruction, even those whose disease has recurred after EBRT.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
59. 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.	7	9,387	Meta-analysis using available randomized trials to evaluate the effect of cytotoxic chemotherapy on survival in patients with NSCLC.	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). 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).	1
60. Grilli R, Oxman AD, Julian JA. Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? *J Clin Oncol* 1993; 11(10):1866-1872.	7 (meta-analysis)	635 patients	To estimate the impact of chemotherapy on survival of patients with advanced NSCLC.	Overall, chemotherapy was associated with a 24% (95% CI, 13%-34%) reduction in the probability of death when compared with supportive care. However, the effect of treatment appeared to decrease significantly after the first 6 months from therapy inception and the mean potential gain in survival, as compared with supportive care, was approximately 6 weeks (95% CI, 1-10). Chemotherapy is effective in the treatment of advanced NSCLC, but its impact on the length of survival is limited. Future RCT should still include an untreated control group and should measure QOL in addition to survival.	2
61. Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F. Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. *Chest* 1994; 106(3):861-865.	7 (meta-analysis)	712 cases	To contribute to the current debate about the relative merits of meta-analysis of the literature and of individual patients data.	Survival probability at 6 months after randomization, as estimated from the published survival curves, has been considered as the end-point of interest. Quality scoring of the studies has also been performed. The estimated pooled odds ratio of death was 0.44, with 95% CI of 0.32-0.59, thus significantly favoring chemotherapy, and it corresponds to an estimated increase in median survival from 3.9 months for BSC to 6.7 for chemotherapy. The results of our individual patient's data, favoring chemotherapy, are in line with those of a meta-analysis recently published. However, they have to be considered in the light of their actual clinical relevance and of the balance between QOL, toxicity, and costs of chemotherapy and BSC.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
62. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. *Lancet* 1993; 342(8862):19-21.	7 (meta-analysis)	706 patients from 7 studies	Meta-analysis of all published polychemotherapy vs supportive care clinical trials in patients with non-resectable non small cell lung cancer.	Analysis showed a reduction in mortality during the first 6 months with polychemotherapy. Although small, this increase in survival, together with an improved QOL, suggests that polychemotherapy should be recommended for patients with non-resectable non small cell lung cancer.	2
63. Cullen MH, Billingham LJ, Woodroffe CM, et al. Mitomycin, ifosfamide, and cisplatin in unresectable non-small-cell lung cancer: effects on survival and quality of life. *J Clin Oncol* 1999; 17(10):3188-3194.	1	797 total patients: 446 MIC1; 351 MIC2	Prospective randomized trial in patients with stage IV NSCLC. Compared outcomes of platinum-based chemotherapy (MIP) plus BSC vs BSC alone for palliation.	MIP arm had increased MST vs BSC (6.7 months vs 4.8 months). Favored platinum-based chemotherapy plus BSC over BSC alone for palliation. MIC chemotherapy prolongs survival in unresectable NSCLC without compromising QOL.	1
64. Socinski MA, Morris DE, Masters GA, Lilenbaum R. Chemotherapeutic management of stage IV non-small cell lung cancer. *Chest* 2003; 123(1 Suppl):226S-243S.	15	N/A	Guideline on chemotherapeutic management for palliation in stage IV NSCLC.	There is an overall improvement in symptoms and QOL with most all platinum-based regimens in stage IV NSCLC. Physicians involved in the evaluation and management of patients with stage IV NSCLC should be aware of the potential benefits of chemotherapy, allowing them to make appropriate recommendations for patients under their care.	4

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
65. Lilenbaum R, Villaflor VM, Langer C, et al. Single-agent versus combination chemotherapy in patients with advanced non-small cell lung cancer and a performance status of 2: prognostic factors and treatment selection based on two large randomized clinical trials. *J Thorac Oncol* 2009; 4(7):869-874.	1	201 patients	To evaluate prognostic factors and treatment selection in the first-line management of advanced NSCLC patients with PS 2 in two randomized trials.	Objective responses were 37% and 15%, respectively. Median time to progression was 4.6 months in the combination arm and 3.5 months in the single-agent arm (P<0.001). MST was 8.0 and 6.6 months, and 1-year survival rates were 31% and 26%, respectively. Albumin <3.5 g, extrathoracic metastases, lactate dehydrogenase ≥200 IU, and 2 comorbid conditions predicted outcome. Patients with 0-2 risk factors had similar outcomes independent of treatment, whereas patients with 3-4 factors had a nonsignificant improvement in median survival with combination chemotherapy. The results show that PS2 NSCLC patients are a heterogeneous group who has significantly different outcomes. Patients treated with first-line combination chemotherapy had a higher response and longer time to progression, whereas OS did not appear significantly different. A prognostic model may be helpful in selecting PS 2 patients for either treatment strategy.	1
66. Roszkowski K, Pluzanska A, Krzakowski M, et al. A multicenter, randomized, phase III study of docetaxel plus best supportive care versus best supportive care in chemotherapy-naive patients with metastatic or non-resectable localized non-small cell lung cancer (NSCLC). *Lung Cancer* 2000; 27(3):145-157.	1	207 patients	Prospective randomized trial of stage IV NSCLC. Compared outcomes of BSC vs Taxotere (docetaxel) + BSC for palliation using EORTC QOL questionnaire (QOL-C30).	Found significant improvement in pain, dyspnea, and emotional functioning in taxotere arm. Taxotere showed good symptom palliation as second-line agent.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
67. Ranson M, Davidson N, Nicolson M, et al. Randomized trial of paclitaxel plus supportive care versus supportive care for patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst* 2000; 92(13):1074-1080.	1	157 total patients: 78 patients supportive care alone; 79 patients paclitaxel plus supportive care	Prospective randomized trial in advanced stage NSCLC to compare outcomes of paclitaxel + BSC vs BSC alone for palliation.	Pretreatment characteristics were evenly distributed between the two arms. Survival was statistically significantly better in the paclitaxel plus supportive care arm than in the supportive care alone arm (two-sided P=.037) (median survival = 6.8 months vs 4.8 months). Cox multivariate analysis showed paclitaxel plus supportive care to be statistically significantly associated with improved survival (two-sided P=.048). QOL was similar for both treatment arms, except for the functional activity score of the Rotterdam Symptom Checklist, where QOL data statistically significantly favored the paclitaxel plus supportive care arm (two-sided P =.043). The addition of paclitaxel to BSC significantly improved survival and time to disease progression compared with BSC in patients with advanced NSCLC and may improve some aspects of QOL.	1

Nonsurgical Treatment for Non-Small-Cell Lung Cancer Poor Performance Status or Palliative Intent
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
68. Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2000; 18(3):623-631.	1	599 patients	Prospective randomized multi-institutional trial of chemotherapy-naïve patients with stage IIIB/IV NSCLC to compare outcomes of paclitaxel + cisplatin vs etoposide + cisplatin for palliation.	Superior survival was observed with the combined paclitaxel regimens (MST, 9.9 months; 1-year survival rate, 38.9%) compared with etoposide plus cisplatin (MST, 7.6 months; 1-year survival rate, 31.8%; P =. 048). Comparing survival for the two dose levels of paclitaxel revealed no significant difference. The median survival duration for the stage IIIB subgroup was 7.9 months for etoposide plus cisplatin patients vs 13.1 months for all paclitaxel patients (P=.152). For the stage IV subgroup, the MST for etoposide plus cisplatin was 7.6 months compared with 8.9 months for paclitaxel (P=.246). With the exceptions of increased granulocytopenia on the low-dose paclitaxel regimen and increased myalgias, neurotoxicity, and, possibly, increased treatment-related cardiac events with high-dose paclitaxel, toxicity was similar across all three arms. QOL declined significantly over the 6 months. However, QOL scores were not significantly different among the regimens. As a result of these observations, paclitaxel (135 mg/m(2)) combined with cisplatin has replaced etoposide plus cisplatin as the reference regimen in our recently completed phase III trial.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
69. Rudd RM, Gower NH, Spiro SG, et al. Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. *J Clin Oncol* 2005; 23(1):142-153.	1	422 total patients: 212 gemcitabine plus carboplatin; 210 MIP	Phase III randomized trial to compare two chemotherapy regimens, gemcitabine plus carboplatin and MIP, in chemotherapy- naïve patients with advanced NSCLC.	There was a significant survival advantage for gemcitabine plus carboplatin compared with MIP (HR, 0.76; 95% CI, 0.61-0. 93; P=.008). Median survival was 10 months with gemcitabine plus carboplatin and 7.6 months with MIP (difference, 2.4 months; 95% CI, 1.0-4.0), and 1-year survival was 40% with gemcitabine plus carboplatin and 30% with MIP (difference, 10%; 95% CI, 3%-18%). Overall response rates were similar (42% for gemcitabine plus carboplatin vs 41% for MIP; P=.84). More thrombocytopenia occurred with gemcitabine plus carboplatin (P=.03), but this was not associated with increased hospital admission or fatality. Gemcitabine plus carboplatin caused less nausea, vomiting, constipation, and alopecia and was associated with fewer admissions for administration and better QOL. In patients with advanced NSCLC, gemcitabine plus carboplatin chemotherapy was shown to be a better-tolerated treatment that conferred a survival advantage over MIP.	1
70. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; 18(10):2095-2103.	1	103 patients	Prospective randomized trial in patients with stage IIIB/IV NSCLC who had failed platinum-based therapy. Compared outcomes of Taxotere + BSC vs BSC alone for palliation.	Significant survival benefit in Taxotere arm (MST 7.5 months vs 4.6 months). One-year survival was 37% in Taxotere arm vs 11% in BSC arm.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
71. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000; 18(12):2354-2362.	1	373 patients	Prospective randomized phase III trial in patients with advanced NSCLC previously treated with platinum-based chemotherapy to compare Taxotere (high and low dose) vs vinorelbine/ifosfamide as second-line palliative treatment.	Overall response rates were 10.8% with D100 and 6.7% with D75, each significantly higher than the 0.8% response with V/I (P=.001 and P=.036, respectively). Patients who received docetaxel had a longer time to progression (P=.046, by log-rank test) and a greater PFS at 26 weeks (P=.005, by chi(2) test). Although OS was not significantly different between the 3 groups, the 1-year survival was significantly greater with D75 than with the control treatment (32% vs 19%; P=.025, by chi(2) test). Prior exposure to paclitaxel did not decrease the likelihood of response to docetaxel, nor did it impact survival. There was a trend toward greater efficacy in patients whose disease was platinum-resistant rather than platinum-refractory and in patients with PS of 0 or 1 vs 2. Toxicity was greatest with D100, but the D75 arm was well-tolerated. This first randomized trial in this setting demonstrates that D75 every 3 weeks can offer clinically meaningful benefit to patients with advanced NSCLC whose disease has relapsed or progressed after platinum-based chemotherapy.	*1*
72. Douillard JY, Giaccone G, Horai T, et al. Improvement in disease-related symptoms and quality of life in patients with advanced non-small-cell lung cancer (NSCLC) treated with ZD1839 (‘Iressa’) (IDEAL 1). *Proc Am Soc Clin Oncol* 2002; 21(pt 1):299a.	1	210 patients	Multi-center randomized phase II trial of patients with advanced NSCLC who had failed platinum-based therapy. Looked at efficacy and toxicity related to 250mg Iressa vs 500 mg Iressa.	Efficacy at both doses was similar. MST in the 250 mg arm was 7.6 months vs 8 months on the 500 mg arm. Objective tumor response rates were 18.4% and 19%. Drug-related toxicities were more frequent in the higher-dose group. ZD1839 provides rapid, significant and clinically meaningful symptom relief and improvements in QOL in NSCLC patients who had previously been treated with platinum-based therapy. The data suggest that symptom improvement, independent of objective tumor response, is associated with a longer PFS and survival. ‘Iressa’ is a trademark of the AstraZeneca group of companies.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
73. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004; 22(11):2184-2191.	1	99 patients	A phase II randomized trial of patients with advanced, metastatic, or recurrent NSCLC to investigate the efficacy and safety of bevacizumab plus carboplatin and paclitaxel in patients with advanced or recurrent NSCLC.	Compared with the control arm, treatment with carboplatin and paclitaxel plus bevacizumab (15 mg/kg) resulted in a higher response rate (31.5% vs 18.8%), longer median time to progression (7.4 vs 4.2 months) and a modest increase in survival (17.7 vs 14.9 months). Of the 19 control patients that crossed over to single-agent bevacizumab, five experienced stable disease, and 1-year survival was 47%. Bleeding was the most prominent adverse event and was manifested in two distinct clinical patterns; minor mucocutaneous hemorrhage and major hemoptysis. Major hemoptysis was associated with squamous cell histology, tumor necrosis and cavitation, and disease location close to major blood vessels. Bevacizumab in combination with carboplatin and paclitaxel improved overall response and time to progression in patients with advanced or recurrent NSCLC. Patients with nonsquamous cell histology appear to be a subpopulation with improved outcome and acceptable safety risks.	1
74. Natale RR, Skarin AT, Maddox AM, et al. Improvement in symptoms and quality of life for advanced non-small-cell lung cancer patients receiving ZD1839 ('Iressa') (IDEAL 2). *Proc Am Soc Clin Oncol* 2002; 21(pt 1):292a.	1	216 patients	Multi-center randomized phase II trial of patients with advanced NSCLC who had failed platinum-based therapy. Looked at efficacy and toxicity related to 250mg Iressa vs 500 mg Iressa. (Follow-up to IDEAL 1).	Study found correlation between symptom improvement and survival benefit. In patients with symptom improvement the median survival (at 9.2 months follow-up) in the 250 mg arm was not reached and was 8.1 months in the 500 mg arm.	1
75. 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.	1	731 patients	To determine whether erlotinib prolongs survival in lung cancer after the failure of first-line or second-line chemotherapy.	Erlotinib can prolong survival.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
76. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006; 355(24):2542-2550.	1	878 patients: 444 chemotherapy with paclitaxel and carboplatin alone; 434 paclitaxel and carboplatin plus bevacizumab	Randomized study to determine the effects of chemotherapy with paclitaxel-carboplatin alone or with bevacizumab for NSCLC.	The median survival was 12.3 months in the group assigned to chemotherapy plus bevacizumab, as compared with 10.3 months in the chemotherapy-alone group (HR for death, 0.79; P=0.003). The median PFS in the two groups was 6.2 and 4.5 months, respectively (HR for disease progression, 0.66; P<0.001), with corresponding response rates of 35% and 15% (P<0.001). Rates of clinically significant bleeding were 4.4% and 0.7%, respectively (P<0.001). There were 15 treatment-related deaths in the chemotherapy-plus-bevacizumab group, including 5 from pulmonary hemorrhage. The addition of bevacizumab to paclitaxel plus carboplatin in the treatment of selected patients with NSCLC has a significant survival benefit with the risk of increased treatment-related deaths.	1
77. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2010; 11(6):521-529.	1	889 patients included in main study: 438 Erlotinib (150 mg/day); 451 placebo	Phase III, placebo-controlled Sequential Tarceva in unresectable NSCLC (SATURN; BO18192) study to assess use of erlotinib as maintenance therapy in patients with non-progressive disease following first-line platinum-doublet chemotherapy.	After a median follow-up of 11.4 months for the erlotinib group and 11.5 months for the placebo group, median PFS was significantly longer with erlotinib than with placebo: 12.3 weeks for patients in the erlotinib group vs 11.1 weeks for those in the placebo group (HR 0.71, 95% CI, 0.62-0.82; P<0.0001). PFS was also significantly longer in patients with EGFR-positive immunohistochemistry who were treated with erlotinib (n=307) compared with EGFR-positive patients given placebo (n=311; median PFS 12.3 weeks in the erlotinib group vs 11.1 weeks in the placebo group; HR 0.69, 0.58-0.82; P<0.0001). Serious adverse events were reported in 47 patients (11%) on erlotinib compared with 34 patients (8%) on placebo. The most common serious adverse event was pneumonia (7 cases [2%] with erlotinib and 4 [<1%] with placebo). Maintenance therapy with erlotinib for patients with NSCLC is well tolerated and significantly prolongs PFS compared with placebo. First-line maintenance with erlotinib could be considered in patients who do not progress after four cycles of chemotherapy.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
78. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. SATURN: A double-blind, randomized, phase III study of maintenance erlotinib versus placebo following nonprogression with first-line platinum-based chemotherapy in patients with advanced NSCLC. *J Clin Oncol* 2009; 27(15s):(suppl; abstr 8001).	1	889 total patients: 438 Erlotinib (150 mg/day); 451 placebo	Phase III SATURN study (BO18192) initiated to evaluate Erlotinib as maintenance therapy after standard first-line platinum-based chemotherapy in advanced NSCLC.	PFS (by investigator assessment; confirmed by independent review) was significantly prolonged with Erlotinib vs placebo in all patients (HR 0.71 [95% CI, 0.62-0.82]; P<.0001) and in EGFR IHC+ patients (HR 0.69 [95% CI, 0.58-0.82]; P<.0001). Response rate was 12% with Erlotinib vs 5% with placebo. Disease control rate (complete response + partial response + stable disease >12 weeks) was 40.8% with Erlotinib vs 27.4% with placebo (P<.0001). OS data are not yet mature. Erlotinib was well tolerated: the majority of treatment-related adverse events were grade 1/2. Adverse events reported in ≥10% of all patients were rash (60% with Erlotinib vs 9% with placebo) and diarrhea (20% with Erlotinib vs 5% with placebo); again, most were grade 1/2. Only 2.3% of patients receiving Erlotinib had a serious treatment-related adverse event and 2.8% withdrew due to a treatment-related adverse event. The SATURN study met its primary and co-primary endpoints with high statistical significance. Erlotinib in the first-line maintenance setting is well tolerated, and significantly improves disease control and delays progression vs placebo across patient subgroups.	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
79. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009; 374(9699):1432-1440.	1	663 patients with stage IIIB or IV disease: 441 pemetrexed (500 mg/m(2), day 1) plus BSC: 222 placebo plus BSC	Randomized double-blind study to assess pemetrexed as maintenance therapy in patients with NSCLC.	Pemetrexed significantly improved PFS (4.3 months [95% CI, 4.1-4.7] vs 2.6 months [1.7-2.8]; HR 0.50, 95% CI, 0.42-0.61, P<0.0001) and OS (13.4 months [11.9-15.9] vs 10.6 months [8.7-12.0]; HR 0.79, 0.65-0.95, P=0.012) compared with placebo. Treatment discontinuations due to drug-related toxic effects were higher in the pemetrexed group than in the placebo group (21 [5%] vs three [1%]). Drug-related grade 3 or higher toxic effects were higher with pemetrexed than with placebo (70 [16%] vs 9 [4%]; P<0.0001), specifically fatigue (22 [5%] vs one [1%], P=0.001) and neutropenia (13 [3%] vs 0, P=0.006). No pemetrexed-related deaths occurred. Relatively fewer patients in the pemetrexed group than in the placebo group received systemic post-discontinuation therapy (227 [51%] vs 149 [67%]; P=0.0001). Maintenance therapy with pemetrexed is well tolerated and offers improved PFS and OS compared with placebo in patients with advanced NSCLC	1

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
80. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; 363(8):733-742.	1	151 patients	Randomized study to examine the effect of introducing palliative care early after diagnosis on patient-reported outcomes and end-of-life care among ambulatory patients with newly diagnosed disease.	27 died by 12 weeks and 107 (86% of the remaining patients) completed assessments. Patients assigned to early palliative care had a better QOL than did patients assigned to standard care (mean score on the FACT-L scale [in which scores range from 0 to 136, with higher scores indicating better QOL], 98.0 vs 91.5; P=0.03). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs 38%, P=0.01). Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs 54%, P=0.05), median survival was longer among patients receiving early palliative care (11.6 months vs 8.9 months, P=0.02). Among patients with metastatic NSCLC, early palliative care led to significant improvements in both QOL and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival.	1

Evidence Table Key

Study Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
    a. Cohort
    b. Cross-sectional
    c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations Key

3D-CRT = 3D-confromal radiation therapy

BSC = Best supportive care

CI = Confidence interval

CT = Computed tomography

DFS = Disease-free survival

EBRT = External beam radiotherapy

EGFR = Epidermal growth factor receptor

HR = Hazard ratio

IFRT = Involved-field radiotherapy

IMRT = Intensity-modulated radiotherapy

MIP = Mitomycin, ifosfamide, and cisplatin

MST = Median survival time

MTD = Maximum tolerated dose

NSCLC = Non-small-cell lung cancer

OS = Overall survival

PFS = Progression-free survival

PS = Performance status

QoL = Quality-of-life

RT = Radiation therapy

SBRT = Stereotactic body radiotherapy

SPECT = Single-photon emission tomography