Early Stage Non-Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Hansen H. Introduction. In: Hansen H, ed. *In Lung Cancer Therapy Annual*. 6th ed. New York: Informa Health Care; 2009:1-6.	Review/Other-Tx	N/A	Book chapter.	N/A	4
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; 62(1):10-29.	Review/Other-Tx	N/A	To provide the expected numbers of new cancer cases and deaths in 2012 nationally and by state, as well as an overview of current cancer statistics using data through 2008 including incidence, mortality and survival rates and trends.	N/A	4
3. American Cancer Society. Lung Cancer (Non-Small Cell). Available at: http://www.cancer.org/cancer/lungcancer-non-smallcell/?utm_source=msn&utm_medium=cpc&utm_campaign=Lung+Cancer&utm_content=Lung+Cancer&utm_term=Small%20Cell%20Lung%20Cancer. Accessed 2 January 2013.	Review/Other-Tx	N/A	To provide information on non-small cell type of lung cancer.	N/A	4
4. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007; 2(8):706-714.	Review/Other-Tx	67,725 cases	Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumors.	Suggestions include additional cutoffs for tumor size, with tumors >7 cm moving from T2 to T3; reassigning the category given to additional pulmonary nodules in some locations; and reclassifying pleural effusion as an M descriptor. In addition, it is suggested that T2b N0 M0 cases be moved from stage IB to stage IIA, T2a N1 M0 cases from stage IIB to stage IIA, and T4 N0-1 M0 cases from stage IIIB to stage IIIA.	4
5. Thorax. In: Greene FL, Page DL, Fleming ID, et al, eds. *AJCC Cancer Staging Handbook.* 6th ed. New York, NY; 2002:191-204.	Review/Other-Tx	N/A	Cancer staging manual.	N/A	4

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6. Donington J, Ferguson M, Mazzone P, et al. American College of Chest Physicians and Society of Thoracic Surgeons Consensus Statement for Evaluation and Management for High-Risk Patients With Stage I Non-small Cell Lung Cancer. *Chest* 2012; 142(6):1620-1635.	Review/Other-Tx	N/A	To develop suggestions for evaluation and treatment of stage I NSCLC.	Pretreatment evaluation should focus primarily on measures of cardiopulmonary physiology, as respiratory failure represents the greatest interventional risk. Alternative treatment options to lobectomy for high-risk patients include sublobar resection with or without brachytherapy, SBRT, and RFA. Each is associated with decreased procedural morbidity and mortality but increased risk for involved lobe and regional recurrence compared with lobectomy, but direct comparisons between modalities are lacking.	4
7. Takizawa T, Haga M, Yagi N, et al. Pulmonary function after segmentectomy for small peripheral carcinoma of the lung. *J Thorac Cardiovasc Surg* 1999; 118(3):536-541.	Observational-Tx	181 total patients: 48 segmentectomy; 133 lobectomy	To compare the pulmonary function after a segmentectomy with that after a lobectomy for small peripheral carcinoma of the lung.	12 months after the operation, the segmentectomy and lobectomy groups had forced vital capacities of 2.67 +/- 0.73 L (mean +/- standard deviation) and 2.57 +/- 0.59 L, which were calculated to be 94.9% +/- 10.6% and 91.0% +/- 13.2% of the preoperative values (P=.14), respectively. The segmentectomy and lobectomy groups had postoperative FEV1s of 1.99 +/- 0.63 L and 1.95 +/- 0.49 L, which were calculated to be 93.3% +/- 10.3% and 87.3% +/- 14.0% of the preoperative values, respectively (P=.03). The multiple linear regression analysis showed that the alternative of segmentectomy or lobectomy was not a determinant for postoperative forced vital capacity but did affect postoperative FEV1. Pulmonary function after a segmentectomy for a good-risk patient is slightly better than that after a lobectomy. However, segmentectomy should be still the surgical procedure for only poor-risk patients because of the difficulty in excluding patients with metastatic lymph nodes from the candidates for the procedure.	1

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8. Bolliger CT, Jordan P, Soler M, et al. Pulmonary function and exercise capacity after lung resection. *Eur Respir J* 1996; 9(3):415-421.	Observational-Tx	68 total patients: 50 lobectomy; 18 pneumonectomy	To compare the effect of lobectomy and pneumonectomy on pulmonary function tests, exercise capacity and perception of symptoms.	3-months after lobectomy, forced vital capacity, FEV1, total lung capacity, transfer factor of the lungs for carbon monoxide and maximal oxygen uptake were significantly lower than preoperative values, increasing significantly from 3 to 6 months after resection. 3-months after pneumonectomy, all parameters were significantly lower than preoperative values and significantly lower than postlobectomy values and did not recover from 3 to 6 months after resection. At 6 months after resection significant deficits persisted in comparison with preoperative: for forced vital capacity 7% and 36%, FEV1 9% and 34%, total lung capacity 10% and 33% for lobectomy and pneumonectomy, respectively; and maximal oxygen uptake 20% after pneumonectomy only. Exercise was limited by leg muscle fatigue in 53% of all patients at preoperative. This was not altered by lobectomy, but there was a switch to dyspnoea as the limiting factor after pneumonectomy (61% of patients at 3 months and 50% at 6 months after resection). Furthermore, pneumonectomy compared to lobectomy led to a significantly smaller breathing reserve (mean +/- standard deviation) (28 +/- 13 vs 37 +/- 16% at 3 months; and 24 +/- 11% vs 33 +/- 12% at 6 months post resection) and lower arterial oxygen tension at peak exercise 10.1 +/- 1.5 vs 11.5 +/- 1.6 kPa (76 +/- 11 vs 86 +/- 12 mmHg) at 3 months; 10.1 +/- 1.3 vs 11.3 +/- 1.6 kPa (76 +/- 10 vs 85 +/- 12 mmHg) at 6 months postresection. Measurements of conventional pulmonary function tests alone overestimate the decrease in functional capacity after lung resection. Exercise capacity after lobectomy is unchanged, whereas pneumonectomy leads to a 20% decrease, probably due to the reduced area of gas exchange.	1

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9. Nezu K, Kushibe K, Tojo T, Takahama M, Kitamura S. Recovery and limitation of exercise capacity after lung resection for lung cancer. *Chest* 1998; 113(6):1511-1516.	Observational-Tx	82 patients: 20 pneumonectomies; 62 lobectomies	To assess the effects of pulmonary resection for lung cancer on postoperative recovery and limitation of exercise capacity.	In the lobectomy group, FEV1 vital capacity, and maximum oxygen consumption decreased significantly 3 months after the operation and improved after more than 6 months, but did not reach the preoperative values. In the pneumonectomy group, FEV1 vital capacity, and maximum oxygen consumption decreased 3 months after the surgery and the values did not recover thereafter. In comparison with preoperative values, the functional percentage losses after more than 6 months for lobectomies and pneumonectomies were 11.2% and 36.1% for FEV1, 11.6% and 40.1% for vital capacity, and 13.3% and 28.1% for maximum oxygen consumption, respectively. Postoperatively, maximal minute ventilation, the maximal heart rate percentage, and maximal oxygen pulse during the exercise test significantly decreased in both the lobectomy and pneumonectomy groups. Nevertheless, maximal minute ventilation and oxygen pulse improved more than 6 months after lobectomy compared with the value at 3 months, but not after pneumonectomy. Breathing reserve did not differ before and after surgery in the lobectomy group, although it decreased significantly after surgery in the pneumonectomy group. Subjectively, postoperative exercise after lobectomy was limited by leg discomfort (64% at more than 6 months after surgery); after pneumonectomy, exercise was limited by dyspnea (60%). These results suggest that there are differences between lobectomy and pneumonectomy for lung cancer in terms of recovery and limitation of exercise capacity.	2

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10. BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. *Thorax* 2001; 56(2):89-108.	Review/Other-Tx	N/A	Guidelines to produce detailed recommendations for the selection and management of patients with potentially operable lung cancer.	These existing guidelines make clear the general need for an assessment of fitness and operability. The purpose of the present work is to increase the precision of these and other recommendations where the evidence allows, and thus to give more detailed advice to physicians, surgeons, and oncologists who manage potentially operable patients.	4
11. Colice GL, Shafazand S, Griffin JP, Keenan R, Bolliger CT. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest* 2007; 132(3 Suppl):161S-177S.	Review/Other-Tx	N/A	Guidelines to provide an evidence-based approach to the preoperative physiologic assessment of a patient being considered for surgical resection of lung cancer.	A careful preoperative physiologic assessment will be useful to identify those patients who are at increased risk with standard lung cancer resection and to enable an informed decision by the patient about the appropriate therapeutic approach to treating their lung cancer. This preoperative risk assessment must be placed in the context that surgery for early-stage lung cancer is the most effective currently available treatment for this disease.	4
12. Silvestri GA, Handy J, Lackland D, Corley E, Reed CE. Specialists achieve better outcomes than generalists for lung cancer surgery. *Chest* 1998; 114(3):675-680.	Observational-Tx	1,583 resections	To determine whether the outcome of patients undergoing lung cancer surgery is different between general surgeons and thoracic surgeons.	One-half of lobectomies and nearly 60% of pneumonectomies were performed by general surgeons. Patients were similar in age, sex, gender, race, and the proportion in each severity of illness subclass. Mortality was significantly higher in patients who underwent lobectomy by general surgeons vs thoracic surgeons (5.3% vs 3.0%; $P<0.05$) and in patients with extreme comorbidities (43.6% vs 25.4%; $P=0.03$) or age >65 years (7.4% vs 3.5%; $P<0.05$). 70% of thoracic surgeons performed >10 cases in the series, whereas 75% of general surgeons performed <10 ($P=0.05$). Logistic regression analysis failed to identify any significant variable that might explain the mortality differences between thoracic surgeons and general surgeons. Mortality is lower for lung cancer resection when the surgery is performed by a thoracic surgeon.	2

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13. Deslauriers J, Ginsberg RJ, Piantadosi S, Fournier B. Prospective assessment of 30-day operative morbidity for surgical resections in lung cancer. *Chest* 1994; 106(6 Suppl):329S-330S.	Review/Other-Tx	783 resections	To determine the prevalence of prospective morbidity and mortality rates associated with resection of lung cancer.	Complications occurred more commonly in men (34.3%, P=0.001), in patients age 60 or older (34.0%, P=0.001), and in patients with a Karnofsky index <9 (44%, P<0.001). There was no significant difference between mortality, significant morbidity rates for lobectomy (28.2%), and pneumonectomy (31.9%), or for simple (28.3%) and extended resection (31.9%). The seemingly higher incidence of major postoperative events reported in this series not only reflects the prospective nature of this analysis but also the fact that over 25% of patients were in other therapeutic trials involving neoadjuvant or postoperative adjuvant regimens. Within that context, these data appear to be a reasonable estimate of modern surgical morbidity rates in the treatment of lung cancer.	4
14. Allen AM, Mentzer SJ, Yeap BY, et al. Pneumonectomy after chemoradiation: the Dana-Farber Cancer Institute/Brigham and Women's Hospital experience. *Cancer* 2008; 112(5):1106-1113.	Observational-Tx	73 patients	To examine the outcomes of pneumonectomy after induction chemoradiotherapy in patients with locally advanced NSCLC.	All patients received radiation (median dose of 54 gray [Gy]) and 69 patients (95%) received concurrent chemotherapy. The median age was 62 years and 43 patients (59%) were male; 37 patients (51%) had American Joint Committee on Cancer stage IIIA NSCLC, 27 (37%) had stage IIIB, 6 had stage IIB, and 4 had stage IV NSCLC because of a resected solitary brain metastasis. A majority (44; 60%) of patients received the combination of carboplatin and paclitaxel, whereas 15 (21%) received the combination of cisplatin and etoposide. 45 patients (62%) underwent left pneumonectomy. With a median follow-up of 28 months, the 1-year and 2-year OS rates were 70% and 49%, respectively. The 30-day and 100-day mortality rates were 6% and 10%, respectively. Only 4/73 patients (6%) died of acute respiratory distress syndrome. The rate of nonfatal treatment-related morbidity was 11%. On univariate analysis, right-sided pneumonectomy was associated with a higher risk of treatment-related mortality (P=.099).	2

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15. Scott WJ, Howington J, Feigenberg S, Movsas B, Pisters K. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132(3 Suppl):234S-242S.	Review/Other-Tx	N/A	Practice guidelines for the treatment of NSCLC stage I and stage II.	Surgical resection remains the treatment of choice for stage I and II NSCLC, although surgical methods continue to evolve. Adjuvant chemotherapy for patients with stage II, but not stage I, NSCLC is well established. RT remains an important treatment for either cases of early stage NSCLC that are medically inoperable or patients who refuse surgery.	4
16. McKenna RJ, Jr., Houck W, Fuller CB. Video-assisted thoracic surgery lobectomy: experience with 1,100 cases. *Ann Thorac Surg* 2006; 81(2):421-425; discussion 425-426.	Review/Other-Tx	1,100 lobectomies in 595 women	To review and assess VATS lobectomy.	There were 9 deaths (0.8%), and none was intraoperative or due to bleeding; 932 patients had no postoperative complications (84.7%). Blood transfusion was required in 45/1,100 patients (4.1%). Length of stay was median 3 days (mean, 4.78).180patients (20%) were discharged on postoperative day 1 or 2. Conversion to a thoracotomy occurred in 28 patients (2.5%). Recurrence developed in the incisions in 5 patients (0.57%). In 2003, 89% of 224 lobectomies were performed with VATS. VATS lobectomy with anatomic dissection can be performed with low morbidity and mortality rates. The risk of intraoperative bleeding or recurrence in an incision seems minimal.	4
17. Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. *J Clin Oncol* 2009; 27(15):2553-2562.	Review/Other-Tx	21 studies	To perform a meta-analysis of the randomized and nonrandomized comparative studies in an attempt to assess the safety and efficacy of VATS lobectomy.	There were no significant statistical differences between VATS and open lobectomy in terms of postoperative prolonged air leak (P=.71), arrhythmia (P=.86), pneumonia (P=.09), and mortality (P=.49). VATS did not demonstrate any significant difference in locoregional recurrence (P=.24), as compared with the open lobectomy arm, but the data suggested a reduced systemic recurrence rate (P=.03) and an improved 5-year mortality rate of VATS (P=.04). There was no evidence to suggest heterogeneity of trial results. 14 studies reported VATS to open lobectomy conversion rate ranging from 0% to 15.7% (median = 8.1%).	4

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18. Manser R, Wright G, Hart D, Byrnes G, Campbell DA. Surgery for early stage non-small cell lung cancer. *Cochrane Database Syst Rev* 2005; (1):CD004699.	Review/Other-Tx	1,910 total patients; 11 trials	To determine whether, in patients with early stage NSCLC, surgical resection of cancer improves disease-specific and all-cause mortality compared with no treatment, RT or chemotherapy. To also compare the effectiveness of different surgical approaches (eg, lobectomy vs limited resection) in improving disease-specific or all-cause mortality in patients with early stage lung cancer.	In a pooled analysis of 3 trials, 4-year survival was superior in patients with resectable stage I to IIIA NSCLC who underwent resection and complete mediastinal lymph node dissection compared with those undergoing resection and lymph node sampling, the HR was estimated to be 0.78 (95% CI, 0.65-0.93, P=0.005). A further trial found an increased rate of local recurrence in patients with stage I NSCLC treated with limited resection compared with lobectomy. One small trial found a survival advantage in favor of chemotherapy followed by surgery compared to chemotherapy followed by RT in patients with stage IIIA NSCLC. However, none of the other trials included in the review demonstrated a significant improvement in survival in patients treated with surgery compared with nonsurgical therapy. Several of the included trials had potential methodological weaknesses. Conclusions about the efficacy of surgery for local and loco-regional NSCLC are limited by the small number of participants studied to date and potential methodological weaknesses of trials. Current evidence suggests that lung cancer resection combined with complete mediastinal lymph node dissection is associated with a small to modest improvement in survival compared with lung cancer resection combined with systematic sampling of mediastinal nodes in patients with stage I to IIIA NSCLC.	4

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19. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006; 81(3):1013-1019; discussion 1019-1020.	Experimental-Tx	1,023 patients: 498 lymph node sampling; 525 lymph node dissection	Randomized trial to compare lymph node sampling vs mediastinal lymph node dissection for early stage lung cancer.	Operative mortality was 2.0% (10/498) for lymph node sampling and 0.76% (4/525) for lymph node dissection. Complications occurred in 38% of patients in each group. Lymph node dissection had a longer median operative time and greater total chest tube drainage (15 minutes, 121 mL, respectively). There was no difference in the median hospitalization, which was 6 days in each group (P=0.404). Complete mediastinal lymphadenectomy adds little morbidity to a pulmonary resection for lung cancer. These data from a current, multi-institutional cohort of patients who underwent a major pulmonary resection constitute a new baseline with which to compare results in the future.	1
20. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2007; 2(7):593-602.	Observational-Tx	18,198 patients	To propose changes in the seventh revision of the tumor, node, metastasis (TNM) classification for lung cancer.	On the basis of the optimal cutpoints, pT1NOR0 was divided into pT1a ≤2 cm (n=1,816) and pT1b >2 to 3 cm (n=1,653) with 5-year survival rates of 77% and 71% (P<0.0001). The pT2NOR0 cutpoints resulted in pT2a >3 to 5 cm (n=2,822), pT2b >5 to 7 cm (n=825), and pT2c >7 cm (n=364). Their 5-year survival rates were 58%, 49%, and 35% (P<0.0001). For clinically staged N0, 5-year survival was 53% for cT1a, 47% for cT1b, 43% for cT2a, 36% for cT2b, and 26% for cT2c. pT3NO (n=711) and pT4 (any N) (n=340) had 5-year survival rates of 38% and 22%. pT4 (additional nodule(s) in the same lobe) (n=363) had a 5-year survival rate of 28%, similar to pT3 (P=0.28) and better than other pT4 (P=0.0029). For pM1 (ipsilateral pulmonary nodules) (n=180), 5-year survival was 22%, similar to pT4. For cT4-malignant pleural effusion/nodules, 5-year survival was 2%. Recommended changes in the T classification are to subclassify T1 into T1a and T1b, and T2 into T2a and T2b; and to reclassify T2c and additional nodule(s) in the same lobe as T3, nodule(s) in the ipsilateral nonprimary lobe as T4, and malignant pleural or pericardial effusions as M1.	2

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21. Choong CK, Meyers BF, Battafarano RJ, et al. Lung cancer resection combined with lung volume reduction in patients with severe emphysema. *J Thorac Cardiovasc Surg* 2004; 127(5):1323-1331.	Observational-Tx	21 patients	To review experience with patients with resectable lung cancer and severe respiratory limitation due to emphysema who may have a suitable operative risk by combining cancer resection with lung volume reduction surgery.	In 9 patients, the cancer was located in a severely emphysematous lobe and the lung volume reduction surgery component of the procedure was accomplished with lobectomy alone. In the remaining 12 patients, the cancer resection lobectomy (n=9) and wedge resection (n=3) were supplemented with lung volume reduction surgery. Final pathologic staging was stage I in 16 patients, stage II in 2 patients, and stage III in 2 patients. One patient was found to have stage IV disease due to multifocal tumors in separate lobes. Postoperative complications included prolonged air leak in 11 patients, atrial fibrillation in 6 patients, and reintubation for ventilatory assistance in 2 patients. All patients showed improved lung function postoperatively. Survival was 100% and 62.7% at 1 and 5 years, respectively. Patients with severe emphysema and resectable lung cancer who have a favorable anatomy for lung volume reduction surgery may undergo a combined cancer resection and lung volume reduction surgery with an acceptable risk and good long-term survival.	2

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22. Shennib H, Bogart J, Herndon JE, et al. Video-assisted wedge resection and local radiotherapy for peripheral lung cancer in high-risk patients: the Cancer and Leukemia Group B (CALGB) 9335, a phase II, multi-institutional cooperative group study. *J Thorac Cardiovasc Surg* 2005; 129(4):813-818.	Observational-Tx	58 patients	Prospective phase II multicenter trial to examine the feasibility of thoracoscopic wedge resection and RT for clinical T1 lesions in patients with compromised cardiopulmonary status.	Resection margins were positive in 5 patients: 6% of T1 and 23% of T2. Surgery was aborted in 2 cases (3.5%), and operative mortality was 4%. Overall operative failure rates of video-assisted wedge resection were 20% for benign T1-size lesions, 22% for T1 NSCLC, 21% for all T1 lesions, 50% for T2 NSCLC, and 29% for all lesions in this study (clinical T1). Prolonged air leaks occurred in 10%, pneumonia in 6%, and respiratory failure in 4%. Thirty-one patients were eligible for RT; 3 of them refused, and 1 died before treatment. Among the 28 patients who received RT, severe dyspnea was noted in 3 patients (11%) and moderate pneumonitis in 4 (14%). Clinical staging in high-risk patients is often inaccurate (45% difference from pathologic staging). Intention to treat clinically staged T1 disease by video-assisted wedge resection is associated with a high failure rate. Pathologically staged T1 lesions can be successfully resected in 75% of cases; however, narrow resection margins remain a concern.	2

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23. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995; 60(3):615-622; discussion 622-613.	Experimental-Tx	246 eligible patients	Prospective, multi-institutional randomized trial to compare limited resection with lobectomy for patients with peripheral T1N0 NSCLC documented at operation.	There was an observed 75% increase in recurrence rates (P=0.02, one-sided) attributable to an observed tripling of the local recurrence rate (P=0.008 two-sided), an observed 30% increase in overall death rate (P=0.08, one-sided), and an observed 50% increase in death with cancer rate (P=0.09, one-sided) compared to patients undergoing lobectomy (P=0.10, one-sided was the predefined threshold for statistical significance for this equivalency study). Compared with lobectomy, limited pulmonary resection does not confer improved perioperative morbidity, mortality, or late postoperative pulmonary function. Because of the higher death rate and locoregional recurrence rate associated with limited resection, lobectomy still must be considered the surgical procedure of choice for patients with peripheral T1 N0 NSCLC.	1
24. Miller JI, Hatcher CR, Jr. Limited resection of bronchogenic carcinoma in the patient with marked impairment of pulmonary function. *Ann Thorac Surg* 1987; 44(4):340-343.	Review/Other-Tx	32 patients	To evaluate limited resection of bronchogenic carcinoma in patients with marked impairment of pulmonary function.	The pathological stage of disease was stage I in 31 patients and stage II in 1 patient. 10 patients were treated by segmental resection and 22 by wide wedge resection. 2-year and 3-year survival is 84% and 78%, respectively, and 10 patients (31%) have survived for 5 years. Recurrent disease developed in 8 patients, 5 of whom died. Recurrence was highest when the lesion crossed an intersegmental plane. In 1978, PORT was added to the treatment of all patients whose lesion crossed an intersegmental plane. Since then, 18 patients have undergone wedge resection and PORT with only 2 local recurrences at 2 years.	4

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25. Santos R, Colonias A, Parda D, et al. Comparison between sublobar resection and 125Iodine brachytherapy after sublobar resection in high-risk patients with Stage I non-small-cell lung cancer. *Surgery* 2003; 134(4):691-697; discussion 697.	Observational-Tx	203 total patients: 102 stage I NSCLC; 101 stage I patients who underwent sublobar resection and intraoperative (125)Iodine brachytherapy	To review researchers' intraoperative (125)Iodine brachytherapy experience after sublobar resection in high-risk stage I NSCLC patients and compares these results with their previous series of sublobar resection alone in similar patients.	Local recurrence after sublobar resection and (125)Iodine brachytherapy (2%) in high-risk stage I NSCLC patients was significantly less than after sublobar resection alone (18.6%). This safe, pulmonary function-preserving and practical intraoperative brachytherapy method should be considered when sublobar resection is used as a "compromise" therapy in these patients.	2
26. McKenna RJ, Jr., Mahtabifard A, Yap J, et al. Wedge resection and brachytherapy for lung cancer in patients with poor pulmonary function. *Ann Thorac Surg* 2008; 85(2):S733-736.	Review/Other-Tx	48 patients	To present technique of sublobar resection combined with afterload catheters for high-dose-rate brachytherapy for patient benefit with minimal risk to others.	Two patients died. The length of mean stay was 5.5 days (median, 5 days). Complications included prolonged air leak in 5 patients, atrial fibrillation in 5, pneumonia in 3, trapped lung in 2, and 1 each with empyema, bleeding, and recurrent laryngeal nerve injury. Three patients required a blood transfusion. Within the follow-up of 1 to 27 months, there were four recurrences. Wedge resection and brachytherapy appears to be a reasonable treatment for patients with lung cancer and pulmonary function that prohibits a lobectomy.	4

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27. Schuchert MJ, Abbas G, Pennathur A, et al. Sublobar Resection for Early-Stage Lung Cancer. *Seminars in Thoracic and Cardiovascular Surgery* 2010; 22(1):22-31.	Review/Other-Tx	428 total patients: 182 segmentectomy; 246 lobectomy	To review past and current studies evaluating sublobar resection with vs without intraoperative brachytherapy in high-risk patients with stage I NSCLC.	Overall recurrence was 28% among lobectomy patients and 27% among segmentectomy patients. At a median follow-up of 31 months, there was no difference in DFS between groups. Tumor size is a recognized prognostic variable in NSCLC and may serve to dictate the extent of resection required. There is accumulating evidence that sublobar resection techniques may achieve similar oncological outcomes when compared with lobectomy in the setting of smaller tumors. Other reports examining sublobar resection in the setting of subcentimeter tumors document no difference in local recurrence or survival. These data support the evolving concept that anatomic sublobar resection (anatomic segmentectomy) can be performed with similar expected survival in select patients with small peripheral tumors (in particular those >2 cm). Sublobar resection can be performed safely in high-risk patients with acceptable morbidity, mortality, recurrence and survival, and may represent a reasonable therapeutic alternative in patients deemed at high risk for lobectomy.	4
28. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet* 1998; 352(9124):257-263.	Review/Other-Tx	9 Trials; 2,128 patients	A systematic review and meta-analysis of the available evidence from randomized trials of PORT.	PORT is detrimental to patients with early-stage completely resected NSCLC and should not be used routinely for such patients. The role of PORT in the treatment of N2 tumors is not clear and may warrant further research.	4
29. Trodella L, Granone P, Valente S, et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. *Radiother Oncol* 2002; 62(1):11-19.	Experimental-Tx	104	Randomized trial to evaluate PORT in completely resected stage I patients.	"Promising trend" of a decrease in local recurrence rate (2.2% vs 23%) and increased DFS rate and OS rate at 5 years, (70% vs 60% and 67% vs 58%) with RT. Treatment related toxicity was felt to be acceptable.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Douillard JY, Rosell R, De Lena M, Riggi M, Hurteloup P, Mahe MA. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys* 2008; 72(3):695-701.	Review/Other-Tx	840 patients	To study the impact of PORT on survival in the Adjuvant Navelbine International Trialist Association (ANITA) randomized study of adjuvant chemotherapy.	Overall, 232 of 840 patients received PORT (33.3% in the observation arm and 21.6% in the chemotherapy arm). In univariate analysis, PORT had a deleterious effect on the overall population survival. Patients with pN1 disease had an improved survival from PORT in the observation arm (median survival 25.9 vs 50.2 months), whereas PORT had a detrimental effect in the chemotherapy group (median survival 93.6 months and 46.6 months). In contrast, survival was improved in patients with pN2 disease who received PORT, both in the chemotherapy (median survival 23.8 vs 47.4 months) and observation arm (median 12.7 vs 22.7 months).	4
31. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004; 350(4):351-360.	Experimental-Tx	1,867	Randomized, multicenter trial to evaluate the effect of cisplatin-based adjuvant chemotherapy on survival after complete resection of NSCLC. Patients were randomly assigned either 3 or 4 cycles of cisplatin-based chemotherapy or to observation.	Patients assigned to chemotherapy had a significantly higher survival rate than those assigned to observation (44.5% vs 40.4% at 5 years [469 deaths vs 504]. Patients assigned to chemotherapy also had a significantly higher DFS rate than those assigned to observation (39.4% vs 34.3% at 5 years [518 events vs 577]. Cisplatin-based adjuvant chemotherapy improves survival among patients with completely resected NSCLC.	1
32. Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer. *J Natl Cancer Inst* 2003; 95(19):1453-1461.	Experimental-Tx	1,209 patients: 606 in mitomycin, vindesine and cisplatin group; 603 controls	Adjuvant Lung Project Italy, a randomized trial to examine the potential benefits of adjuvant chemotherapy for survival. Stage I, II, IIIA NSCLC after complete resection randomized to 3 cycles of mitomycin, vindesine and cisplatin or no further treatment.	No statistically significant difference between the 2 groups in OS (HR = 0.96, 95% CI 0.81 to 1.13; P=.589) or PFS (HR = 0.89, 95% CI 0.76 to 1.03; P=.128). Trial failed to confirm the effectiveness of adjuvant chemotherapy for patients with NSCLC.	1
33. Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004; 26(1):173-182.	Experimental-Tx	381 patients; 92 received chemotherapy 189 patients no chemotherapy	To run a large randomized trial to confirm the survival benefits seen in the meta-analysis that suggest a survival benefit for cisplatin-based chemotherapy when given in addition to surgery, radical RT or 'best supportive care'.	198 (52%) of patients have died, but there is currently no evidence of a benefit in OS to the chemotherapy group: HR 1.02 (95% CI 0.77-1.35), P=0.90).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005; 352(25):2589-2597.	Experimental-Tx	482	Randomized trial to determine whether adjuvant vinorelbine plus cisplatin prolongs OS among patients with completely resected early-stage NSCLC. Patients were randomly assigned to vinorelbine plus cisplatin or to observation.	OS was significantly prolonged in the chemotherapy group compared with the observation group (94 vs 73 months. 5-year survival rates were 69 % and 54 %, respectively (P=0.03).Adjuvant vinorelbine plus cisplatin has an acceptable level of toxicity and prolongs DFS and OS rates among patients with completely resected early-stage NSCLC.	1
35. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol* 2006; 7(9):719-727.	Experimental-Tx	840 patients	To compare the effect of adjuvant vinorelbine plus cisplatin vs observation on survival in patients with completely resected NSCLC.	367 patients in the chemotherapy group and 431 in the control group received their assigned treatment. 301 (36%) patients had stage IB disease, 203 (24%) had stage II disease, and 325 (39%) had stage IIIA disease. Tolerance to chemotherapy mainly included neutropenia in 335 (92%) patients and febrile neutropenia in 34 (9%); seven (2%) toxic deaths were also recorded. Compliance was greater with cisplatin than with vinorelbine (median dose intensity 89% [range 17-108] vs 59% [17-100]). After a median follow-up of 76 months (range 43-116), median survival was 65.7 months (95% CI 47.9-88.5) in the chemotherapy group and 43.7 (35.7-52.3) months in the observation group. Adjusted risk for death was significantly reduced in patients assigned chemotherapy compared with controls (HR 0.80 [95% CI 0.66-0.96]; P=0.017). OS at 5 years with chemotherapy improved by 8.6%, which was maintained at 7 years (8.4%).	1
36. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008; 26(21):3552-3559.	Review/Other-Tx	7,465	Retrospective study to examine the association between survival and PORT in patients with resected NSCLC. Patients were selected from the SEER database.	PORT did not have a significant impact on survival, but for patients with N2 nodal disease, PORT was associated with a significant increase in survival. For patients with N0 (HR = 1.176; 95% CI 1.005 to 1.376; P=.0435) and N1 (HR = 1.097; 95% CI 1.015 to 1.186; P=.0196) nodal disease, PORT was associated with a significant decrease in survival.	4

Early Stage Non-Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
37. Strauss GM, Herndon JE, Maddaus MA, et al. Adjuvant Paclitaxel Plus Carboplatin Compared With Observation in Stage IB Non–Small-Cell Lung Cancer: CALGB 9633 With the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *Journal of Clinical Oncology* 2008; 26(31):5043-5051.	Experimental-Tx	344 total patients	Randomized trial to evaluate adjuvant paclitaxel plus carboplatin compared with observation in stage IB NSCLC.	Median follow-up was 74 months. Groups were well-balanced with regard to demographics, histology, and extent of surgery. Grades 3 to 4 neutropenia were the predominant toxicity; there were no treatment-related deaths. Survival was not significantly different (HR, 0.83; CI, 0.64 to 1.08; P=.12). However, exploratory analysis demonstrated a significant survival difference in favor of adjuvant chemotherapy for patients who had tumors ≥4 cm in diameter (HR, 0.69; CI, 0.48 to 0.99; P=.043). Because a significant survival advantage was not observed across the entire cohort, adjuvant chemotherapy should not be considered standard care in stage IB NSCLC. Given the magnitude of observed survival differences, CALGB 9633 was underpowered to detect small but clinically meaningful improvements. A statistically significant survival advantage for patients who had tumors ≥4 cm supports consideration of adjuvant paclitaxel/carboplatin for stage IB patients who have large tumors.	1
38. Wakelee H, Dubey S, Gandara D. Optimal adjuvant therapy for non-small cell lung cancer--how to handle stage I disease. *Oncologist* 2007; 12(3):331-337.	Review/Other-Tx	N/A	To review the results of three phase III studies using cisplatin-based regimens–the International Adjuvant Lung Trial, the National Cancer Institute of Canada JBR10 trial, and the Adjuvant Navelbine International Trialist Association trial.	Updated results from the Cancer and Leukemia Group B 9633 trial, the only trial to focus exclusively on stage IB patients, no longer show a statistically significant survival benefit from adjuvant chemotherapy in this population, except for the subgroup of patients with larger tumors. It may be that trials have been underpowered to detect a small benefit for patients with stage IB disease, or there may really not be benefit to adding adjuvant therapy for this stage of disease. Additional markers, such as tumor size or the presence or absence of certain tumor proteins like ERCC1, may help to determine which patients with resected stage I NSCLC may benefit from adjuvant chemotherapy. Strategies such as inhibition of angiogenesis pathways and the epidermal growth factor receptor are under exploration.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
39. Tanaka F, Wada H, Fukushima M. UFT and S-1 for treatment of primary lung cancer. *Gen Thorac Cardiovasc Surg* 2010; 58(1):3-13.	Review/Other-Tx	N/A	To summarize the mechanism of action of UFT and S-1 as well as clinical evidence regarding their use in the treatment of NSCLC.	UFT has proved to be effective in a postoperative adjuvant setting for early NSCLC in several randomized controlled studies. S-1, in which a more potent DPD inhibitor is combined, is active in advanced NSCLC regardless of the histological cell subtype, and its clinical efficacy in first-line therapy for unresectable advanced disease as well as in postoperative adjuvant therapy for resected disease is now being examined in a variety of randomized controlled studies.	4
40. Wisnivesky JP, Bonomi M, Henschke C, Iannuzzi M, McGinn T. Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer. *Chest* 2005; 128(3):1461-1467.	Observational-Tx	4,357 patients	To compare the survival of those treated with radiation alone to those left untreated.	The survival of patients with lung cancer who did not undergo resection and had been treated with RT was significantly better compared to the untreated patients (stage I cancer, P=0.0001; stage II cancer, P=0.001). The median survival time of patients with stage I disease who underwent RT was 21 months compared to 14 months for untreated patients. Stage II patients who received and did not receive RT had median survival times of 14 and 9 months, respectively. The survival of treated and untreated patients was not significantly different approximately 5 years after diagnosis (stage I disease, 15% vs 14%, respectively; stage II disease, 11% vs 10%, respectively). In multivariate analysis, RT was significantly associated with improved lung cancer survival after controlling for age, sex, race, and tumor histology.	2

Early Stage Non-Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
41. McGarry RC, Song G, des Rosiers P, Timmerman R. Observation-only management of early stage, medically inoperable lung cancer: poor outcome. *Chest* 2002; 121(4):1155-1158.	Observational-Tx	128 patients: 49 patients received no cancer treatment; 36 patients received RT only; 43 patients were treated with primary surgery	Retrospective study to assess the treatments received and outcomes of patients with early stage NSCLC.	Median +/- standard deviation survival time following surgery was 46.2 +/- 3.15 months; for no treatment, 14.2 +/- 2.37 months (P=3.2 x 10(-6)); and RT alone, 19.9 +/- 5.6 months (P=0.0005). Of those who received no specific cancer treatment, 14 patients refused treatment and the remainder were not treated for a variety of medical reasons. Cause of death was cancer in 53% of untreated patients and 43% for those receiving RT. RT was administered for postobstructive atelectasis, hemoptysis, increasing tumor size, pain, pleural effusion, and medical inoperability. Radiation dosages had no apparent standard. No significant differences in survival were found for patients receiving RT with either curative or palliative intent (20.3 months vs 16.0 months, respectively; P=0.229). Within the limitations of this retrospective study, it appears that untreated early stage lung cancer has a poor outcome, with >50% of patients dying of lung cancer. Surgery remains the treatment of choice, but lung cancer screening programs will result in increasing numbers of medically inoperable patients with no clear policies for their management.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Qiao X, Tullgren O, Lax I, Sirzen F, Lewensohn R. The role of radiotherapy in treatment of stage I non-small cell lung cancer. *Lung Cancer* 2003; 41(1):1-11.	Review/Other-Tx	N/A	To retrospectively evaluate the role of RT for stage I NSCLC, as a curative modality.	Generally, smaller tumor size, low T-stage and increased dose had a favorable impact on local control and increased local control was followed by increased survival. No serious treatment complications were recorded in the majority of these studies. Overall treatment results were, however, disappointing. The median survival in these studies ranged from 18 to 33 months. The 3- and 5-year OS was 34 +/- 9% and 21 +/- 8% (mean value +/- 1 S.E.), respectively. The cause-specific survival at 3 and 5 years was 39 +/- 10% and 25 +/- 9% (mean value +/- 1 S.E.), respectively. Dose escalation, in a setting with conformal RT using involved field or stereotactic RT, should be the focus of developmental therapeutic strategies with inoperable stage I NSCLC to improve local control and survival.	4
43. Sibley GS. Radiotherapy for patients with medically inoperable Stage I nonsmall cell lung carcinoma: smaller volumes and higher doses--a review. *Cancer* 1998; 82(3):433-438.	Review/Other-Tx	10 studies	Review to summarize findings from published series of RT for patients with medically inoperable stage I NSCLC.	RT doses were similar throughout the series, with a median dose of 60-66 Gy. However, treatment volumes varied considerably, from small “postage stamp” fields to comprehensive lymph node coverage. Averaging the results of these studies showed that approximately 15% of patients will be long-term survivors, 25% will die of intercurrent disease, 30% will die of distant metastatic disease and 30% will die after local failure only. Eight of ten series report Grade 3-5 complications occurring in <2% of patients. Analysis of treatment factors affecting survival revealed a consistent benefit of higher RT doses in terms of local control or DFS. No benefit from prophylactic lymph node irradiation was demonstrated. Despite the infirm nature of patients with medically inoperable stage I NSCLC, the majority will ultimately die of uncontrolled lung carcinoma. Because complications are uncommon after doses of 60-66 Gy, trials of dose escalation to limited fields are indicated for patients with medically inoperable NSCLC in an attempt to improve OS.	4

Early Stage Non-Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Bogart JA, Hodgson L, Seagren SL, et al. Phase I study of accelerated conformal radiotherapy for stage I non-small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904. *J Clin Oncol* 2010; 28(2):202-206.	Observational-Tx	39 patients	To define the maximally accelerated course of conformal RT and to describe the short-term and long-term toxicity of therapy.	39 eligible patients were accrued (8 patients each on cohorts 1 to 4 and 7 patients on cohort 5) between January 2001 and July 2005. One grade 3 nonhematologic toxicity was observed in both cohorts 3 (dyspnea) and cohort 4 (pain). The major response rate was 77%. After a median follow-up time of 53 months, the actuarial median survival time of all eligible patients was 38.5 months. Local relapse was observed in three patients.	1
45. Nagata Y, Takayama K, Matsuo Y, et al. Clinical outcomes of a phase I/II study of 48 Gy of stereotactic body radiotherapy in 4 fractions for primary lung cancer using a stereotactic body frame. *Int J Radiat Oncol Biol Phys* 2005; 63(5):1427-1431.	Observational-Tx	45 patients: 32 stage IA; 13 stage IB lung cancer	To evaluate the clinical outcomes of 48 Gy of 3D SBRT in 4 fractions for treating stage I lung cancer using a stereotactic body frame.	7 tumors (16%) completely disappeared after treatment and 38 tumors (84%) decreased in size by 30% or more. Therefore, all tumors showed local response. During the follow-up of 6-71 (median = 30) months, no pulmonary complications greater than an National Cancer Institute-Common Toxicity Criteria of Grade 3 were noted. No other vascular, cardiac, esophageal, or neurologic toxicities were encountered. Forty-four (98%) of 45 tumors were locally controlled during the follow-up period. However, regional recurrences and distant metastases occurred in 3 and 5 of T1 patients and zero and 4 of T2 patients, respectively. For stage IA lung cancer, the DFS and OS rates after 1 and 3 years were 80% and 72%, and 92% and 83%, respectively, whereas for stage IB lung cancer, the DFS and OS rates were 92% and 71%, and 82% and 72%, respectively. Forty-eight Gy of 3D SBRT in 4 fractions using a stereotactic body frame is useful for the treatment of stage I lung tumors.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
46. Baumann P, Nyman J, Lax I, et al. Factors important for efficacy of stereotactic body radiotherapy of medically inoperable stage I lung cancer. A retrospective analysis of patients treated in the Nordic countries. *Acta Oncol* 2006; 45(7):787-795.	Observational-Tx	138 patients	To review the results of SBRT treatment of patients with medically inoperable stage I NSCLC treated during 1996-2003 at five different centers in Sweden and Denmark.	Mean gross tumor volume was 39cm^3 (2-436), and PTV was 101 cm^3 (11-719). Overall response rate was 61% (84/138). Standard deviation was noted in 36% (50/138). During a median follow-up period of 33 months (1-107), 16 (12%) local failures occurred, 10 of which also included distant metastases. Local failure was associated with tumor size, target definition and central or pleura proximity. Distant metastases occurred in 25% (35/138) of the patients. 91 (65%) patients died during follow-up of which 55 patients (60%) died of other causes than lung cancer. 3-year and 5-year OS was 52% and 26%, respectively. Lung cancer specific 3- and 5-year OS was 66% and 40%, respectively. 59% (83/138) of the patients had no side effects. 14 patients experienced grade 3-4 toxicity according to RTOG. EQD2 (> vs <55.6 Gy) showed a statistically significant benefit survival for the higher doses. SBRT for stage I NSCLC results in favorable local control not inferior to fractionated RT and with acceptable toxicity.	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
47. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009; 75(3):677-682.	Observational-Tx	70 patients	To report the 50-month results of a prospective Phase II trial of SBRT in medically inoperable patients.	Median follow-up was 50.2 months (range, 1.4-64.8 months). Kaplan-Meier local control at 3 years was 88.1%. Regional (nodal) and distant recurrence occurred in 6 (8.6%) and 9 (12.9%) patients, respectively. Median survival was 32.4 months and 3-year OS was 42.7% (95% CI, 31.1%-54.3%). Cancer-specific survival at 3 years was 81.7% (95% CI, 70.0%-93.4%). For patients with T1 tumors, median survival was 38.7 months (95% CI, 25.3-50.2) and for T2 tumors median survival was 24.5 months (95% CI, 18.5-37.4) (P=0.194). Tumor volume (≤5 cc, 5-10 cc, 10-20 cc, >20 cc) did not significantly impact survival: median survival was 36.9 months (95% CI, 18.1-42.9), 34.0 (95% CI, 16.9-57.1), 32.8 (95% CI, 21.3-57.8), and 21.4 months (95% CI, 17.8-41.6), respectively (P=0.712). There was no significant survival difference between patients with peripheral vs central tumors (median survival 33.2 vs 24.4 months, P=0.697). Grade 3 to 5 toxicity occurred in 5/48 patients with peripheral lung tumors (10.4%) and in 6/22 patients (27.3%) with central tumors (Fisher's exact test, P=0.088). Based on the study results, use of SBRT results in high rates of local control in medically inoperable patients with stage I NSCLC.	2

Early Stage Non-Small-Cell Lung Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
48. Fowler JF, Tome WA, Fenwick JD, Mehta MP. A challenge to traditional radiation oncology. *Int J Radiat Oncol Biol Phys* 2004; 60(4):1241-1256.	Review/Other-Tx	N/A	To investigate and compare the BEDs, equivalent doses in 2 Gy fractions, log tumor cells killed, and late effects that can be estimated for the large fractions in short overall times that are now being delivered in various clinically used schedules in several countries for the treatment of cancer in human lungs, liver, and kidney.	Tumor cell kill varies between 16 and 27 logs to base 10 for schedules from 4F x 12 Gy to 3F x 23 Gy. The rationale for the high end of this scale is the possible presence of hypoxic or otherwise extraordinarily resistant cells, but how many tumors and which ones require such doses is not known. How can such large doses be tolerated? In "parallel type organs" it is shown to be theoretically possible, provided that suitably small volumes are irradiated, with rapid fall-off of dose outside the PTV, and a mean dose (excluding PTV and allowing for local fraction size) to both lungs of less than 19 Gy normalized total doses. If suitably small PTV were used, local late BEDs have been given which were as large as 600 Gy(3), equivalent to 2 Gy x 180F = 360 Gy in 2-Gy fractions, with remarkably few complications reported clinically. Questions of concurrent chemotherapy and microscopic extension of lung tumor cells are discussed briefly. Such large doses can apparently be given, with suitable precautions and experience. Ongoing clinical trials from an increasing number of centers will be reporting the results of tumor control and complications from this new modality of biologically higher doses.	4

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
49. Guckenberger M, Wulf J, Mueller G, et al. Dose-response relationship for image-guided stereotactic body radiotherapy of pulmonary tumors: relevance of 4D dose calculation. *Int J Radiat Oncol Biol Phys* 2009; 74(1):47-54.	Observational-Tx	124 patients with 159 pulmonary lesions: 118 metastases; 41 NSCLC (13 stage IA; 19 stage IB, 9 T3N0)	To evaluate outcome after image-guided SBRT for early-stage NSCLC and pulmonary metastases.	With mean/median follow-up of 18/14 months, actuarial local control was 83% at 36 months with no difference between NSCLC and metastases. The dose to the CTV based on 4D dose calculation was closely correlated with local control: local control rates were 89% and 62% at 36 months for >100 Gy and <100 Gy BEDs (P=0.0001), respectively. Actuarial freedom from regional and systemic progression was 34% at 36 months for primary NSCLC group; crude rate of regional failure was 15%. 3-year OS was 37% for primary NSCLC and 16% for metastases; no dose-response relationship for survival was observed. Exacerbation of comorbidities was the most frequent cause of death for primary NSCLC. Doses of >100 Gy BEDs to the CTV based on 4D dose calculation resulted in excellent local control rates. This cutoff dose is not specific to the treatment technique and protocol of our study and may serve as a general recommendation.	2
50. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008; 70(3):685-692.	Observational-Tx	206 patients	To evaluate early clinical outcomes of "risk-adapted" fractionation schemes in patients treated in a single institution.	Median OS was 34 months, with 1- and 2-year survivals of 81% and 64%, respectively. DFS at 1 and 2 years was 83% and 68%, respectively, and DFS correlated with T stage (P=0.002). Local failure was observed in 7 patients (3%). The crude regional failure rate was 9%; isolated regional recurrence was observed in 4%. The distant progression-free survival at 1 and 2 years was 85% and 77%, respectively. SBRT was well tolerated and severe late toxicity was observed in <3% of patients. SBRT is well tolerated in patients with extensive comorbidity with high local control rates and minimal toxicity. Early outcomes are not inferior to those reported for conventional RT. In view of patient convenience, such risk-adapted SBRT schedules should be considered treatment of choice in patients presenting with medically inoperable stage I NSCLC.	2

Early Stage Non-Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
51. 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.	Observational-Tx	257 patients from 14 institutions	Retrospective study to analyze the treatment outcome of HypoFXSRT 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 BED 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 BED of 100 Gy or more compared with 30.2% among those treated with <100 Gy (P<0.05). Although this is a retrospective study, HypoFXSRT with a BED of <180 Gy was almost safe for stage I NSCLC, and the local control and OS rates in 5 years with a BED of 100 Gy or more were superior to the reported results for conventional RT. For all treatment methods and schedules, the local control and survival rates were better with a BED of 100 Gy or more compared with <100 Gy.	2
52. Stephans KL, Djemil T, Reddy CA, et al. A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience. *J Thorac Oncol* 2009; 4(8):976-982.	Observational-Tx	94 consecutive SBRT treatments	To assess the impact of fractionation upon tumor control and toxicity in medically inoperable early stage lung cancer patients treated with SBRT.	Median age was 73 years and median Karnofsky performance status 80. A total of 69 lesions were T1, 24 were T2 lung cancer. Median follow-up was 15.3 months. For the 50- and 60-Gy cohorts at 1 year, local control was 97.3% vs 100%, nodal failure 7.3% vs 3.4%, distant metastasis rate 21.8% vs 29.5%, and OS 83.1% vs 76.9% (P=0.68, 0.54, 0.56, and 0.54, respectively). There was no difference in OS for patients with histologic (n=61) compared with radiographic (n=33) diagnosis. There was no impact of fractionation in the subset of T2 tumors. We observed two cases (2.2%) of clinical grade 2 pneumonitis. Mild late CW toxicity (grade 1 or 2) was seen in 9 patients (10%) at a median of 8.4 months after treatment and was more common in the 60-Gy group (7/38 [18%] vs 2/56 [4%], P=0.028). Local control, OS, nodal failure, and distant failure were not affected by fractionation. CW toxicity was more common with 60-Gy group.	2

Early Stage Non-Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
53. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; 24(30):4833-4839.	Observational-Tx	70	Prospective phase 11 trial using SBRT in medically inoperable early-stage lung cancer.	Kaplan-Meier local control at 2 years was 95%. Median survival was 32.6 months and 2-year OS was 54.7%. Grade 3 to 5 toxicity occurred in 14 patients. Among patients experiencing toxicity, the median time to observation was 10.5 months. Patients treated for tumors in the peripheral lung had 2-year freedom from severe toxicity of 83% compared with only 54% for patients with central tumors. Achieved high rates of local control.	2
54. Timmerman R, Papiez L, McGarry R, et al. Extracranial stereotactic radioablation: results of a phase I study in medically inoperable stage I non-small cell lung cancer. *Chest* 2003; 124(5):1946-1955.	Observational-Tx	37 patients	To investigate a new therapy akin to brain radiosurgery called extracranial stereotactic radioablation in a phase I trial.	Both T-stage groups ultimately reached and tolerated 2,000 cGy per fraction for three fractions (total, 6,000 cGy). The maximum tolerated dose for this therapy in either T-stage group has yet to be reached. Tumors responded to treatment in 87% of patients (complete response, 27%). After a median follow-up period of 15.2 months, six patients experienced local failure, all of whom had received doses of <1,800 cGy per fraction. Very high radiation dose treatments were tolerated in this population of medically inoperable patients with stage I NSCLC using extracranial stereotactic radioablation techniques.	1
55. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010; 303(11):1070-1076.	Observational-Tx	55 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

Early Stage Non-Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
56. Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. *Int J Radiat Oncol Biol Phys* 2001; 51(3):666-670.	Observational-Tx	50 patients	To evaluate CT-guided frameless stereotactic RT for stage I NSCLC.	With a median follow-up period of 36 months (range 22-66), 30 patients were alive and disease free, 3 were alive with disease, 6 had died of disease, and 11 had died intercurrently. Local progression was not observed on follow-up CT scans in 47 (94%) of 50 patients. The 3-year OS rate was 66% in all 50 patients and 86% in the 29 medically operable patients. The 3-year cause-specific survival rate of all 50 patients was 88%. No definite adverse effects related to stereotactic RT were noted, except for 2 patients with a minor bone fracture and 6 patients with temporary pleural pain. Stereotactic RT is a very safe and effective treatment for stage I NSCLC. Additional studies involving a larger patient population and longer follow-up periods are warranted to assess this new treatment for early-stage lung cancer.	2
57. Wulf J, Baier K, Mueller G, Flentje MP. Dose-response in stereotactic irradiation of lung tumors. *Radiother Oncol* 2005; 77(1):83-87.	Observational-Tx	92 pulmonary tumors: 36 NSCLC; 56 metastases	To evaluate the dose-response for local tumor control after stereotactic RT.	After a median follow-up of 14 months (2-85 months) 11 local recurrences were observed with significant advantage for higher doses. When normalization to a BED is used a dose of 94 Gy at the isocenter and 50 Gy at the PTV-margin are demonstrated to give 50% probability of tumor control. Multivariate analysis revealed the dose at the PTV-margin as the only significant factor for local control.	2

Early Stage Non-Small-Cell Lung Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
58. Senthi S, Lagerwaard FJ, Haasbeek CJ, Slotman BJ, Senan S. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012; 13(8):802-809.	Review/Other-Tx	676 patients	To assess patterns of late disease recurrence outcomes after stereotactic ablative RT in a cohort of patients with NSCLC.	The median follow-up was 32.9 months (IQR 14.9-50.9 months). 124 (18%) of 676 patients had disease recurrence. Actuarial 2-year rates of local, regional, and distant recurrence were 4.9% (95% CI 2.7-7.1), 7.8% (5.3-10.3), and 14.7% (11.4-18.0), respectively. Corresponding 5-year rates were 10.5% (95% CI 6.4-14.6), 12.7% (8.4-17.0), and 19.9% (14.9-24.6), respectively. Of the 124 recurrences, 82 (66%) were distant recurrences and 57 (46%) were isolated distant recurrences. Isolated locoregional recurrences occurred in the remaining 42 patients with disease recurrence (34%), 35 (83%) of whom did not develop subsequent distant recurrence. The median times to local, regional, and distant recurrence were 14.9 months (95% CI 11.4-18.4), 13.1 months (7.9-18.3), and 9.6 months (6.8-12.4), respectively. New pulmonary lesions characterized as second primary tumors in the lung developed in 42 (6%) of 676 patients at a median of 18.0 months (95% CI 12.5-23.5) after stereotactic ablative RT.	4
59. Chang JY, Liu H, Balter P, et al. Clinical outcome and predictors of survival and pneumonitis after stereotactic ablative radiotherapy for stage I non-small cell lung cancer. *Radiat Oncol* 2012; 7:152.	Observational-Tx	130 patients	To identify predictors of survival and pneumonitis after stereotactic ablative RT for NSCLC in a relatively large single-institution series.	At a median follow-up time of 26 months, the 2-year local control rate was 98.5%. The median OS time was 60 months, and OS rates were 93.0% at 1 year, 78.2% at 2 years, and 65.3% at 3 years. No patient experienced grade 4-5 toxicity; 15 had radiation pneumonitis (12 [9.3%] grade 2 and 3 [2.3%] grade 3). Performance status, SUVmax on staging PET/CT, tumor histology, and disease operability were associated with OS on univariate analysis, but only staging SUVmax was independently predictive on multivariate analysis (P=0.034). Dosimetric factors were associated with radiation pneumonitis on univariate analysis, but only mean ipsilateral lung dose ≥9.14 Gy was significant on multivariate analysis (P=0.005).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
60. Chetty IJ, Curran B, Cygler JE, et al. Report of the AAPM Task Group No. 105: Issues associated with clinical implementation of Monte Carlo-based photon and electron external beam treatment planning. *Med Phys* 2007; 34(12):4818-4853.	Review/Other-Tx	N/A	A preliminary report to review the tenets of the Monte Carlo method and to provide the framework upon which to build a comprehensive program for commissioning and routine quality assurance of Monte Carlo-based treatment planning systems.	No results stated in abstract.	4
61. Xiao Y, Papiez L, Paulus R, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009; 73(4):1235-1242.	Review/Other-Tx	20 patients	To determine the dose prescription and critical structure constraints for future SBRT lung protocols that mandate density-corrected dose calculations.	With heterogeneity corrections applied, the planning target volume receiving ≥60 Gy decreased, on average, 10.1% (standard error, 2.7%) from 95% (P=.001). The maximal dose to any point ≥2 cm away from the planning target volume increased from 35.2 Gy (standard error, 1.7) to 38.5 Gy (standard error, 2.2).	4
62. Bezjak A. Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0813. Accessed 9 May 2013.	Review/Other-Tx	Ongoing	To compare the overall survival of patients treated with high-dose vs standard-dose conformal radiation therapy in the setting of concurrent chemotherapy; To compare the overall survival of patients treated with cetuximab vs without cetuximab in the setting of concurrent chemotherapy. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0813.	This trial is still recruiting study subjects and results are not available yet.	4
63. Bradley J. A Randomized Phase III Comparison of Standard- Dose (60 Gy) Versus Highdose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab (IND #103444) in Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0617. Accessed 9 May 2013.	Review/Other-Tx	Ongoing	Phase I Portion: To determine the maximal tolerated dose of SBRT for centrally-located NSCLC and the efficacy of that dose in patients who are not operative candidates. Phase II Portion: To estimate the primary tumor control rate at the maximal tolerated dose of SBRT. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0617.	This trial is still recruiting study subjects and results are not available yet.	4

Early Stage Non-Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
64. Videtic GMM. A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients with Stage I Peripheral Non-Small Cell Lung Cancer. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0915. Accessed 9 May 2013.	Review/Other-Tx	Ongoing	To determine the rate of 1-year grade 3 or higher adverse events definitely, probably, or possibly related to treatment. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0915.	This trial is still recruiting study subjects and results are not available yet.	4
65. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys* 2010; 37(8):4078-4101.	Review/Other-Tx	N/A	A review of the literature to identify reported clinical findings and expected outcomes for SBRT.	No results stated in abstract.	4
66. Bral S, Gevaert T, Linthout N, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a Phase II trial. *Int J Radiat Oncol Biol Phys* 2011; 80(5):1343-1349.	Observational-Tx	40 patients	Phase II prospective trial to evaluate a risk adapted strategy of SBRT for early-stage NSCLC.	The lung toxicity-free survival estimate at 2 years was 74% and was related to the location (central vs peripheral) and the size of the target volume. No dose volumetric parameters could predict the occurrence of lung toxicity. One patient died because of treatment-related toxicity. The 1-year and 2-year local progression-free survival estimates were 97% and 84%, respectively, and were related to stage (T1 vs T2) related (P=0.006). Local failure was not more frequent for patients treated in 4 fractions. The 1-year local progression-free survival estimate dropped below 80% for lesions with a diameter of more than 4 cm. The proposed risk-adapted strategy for both centrally and peripherally located lesions showed an acceptable toxicity profile while maintaining excellent local control rates. The correlation between local control and tumor diameter calls for the inclusion of tumor stage as a variable in future study design.	2

Early Stage Non-Small-Cell Lung Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
67. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008; 72(4):967-971.	Observational-Tx	27 patients: 13 with stage I; 14 with isolated recurrent NSCLC	To evaluate the efficacy and adverse effects of image-guided SBRT in centrally/superiorly located NSCLC.	With a median follow-up of 17 months (range, 6-40 months), the crude local control at the treated site was 100% using 50 Gy. Of the patients with recurrent disease, 3 (21.4%) and 5 (35.7%) developed mediastinal lymph node metastasis and distant metastasis, respectively. Four patients (28.6%) with recurrent disease but none with stage I disease developed Grade 2 pneumonitis. Three patients (11.1%) developed Grade 2-3 dermatitis and CW pain. One patient developed brachial plexus neuropathy. No esophagitis was noted in any patient. Image-guided SBRT using 50 Gy delivered in 4 fractions is feasible and resulted in excellent local control.	2
68. Dunlap NE, Cai J, Biedermann GB, et al. Chest wall volume receiving >30 Gy predicts risk of severe pain and/or rib fracture after lung stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; 76(3):796-801.	Observational-Tx	60 patients	To identify the dose-volume parameters that predict the risk of CW pain and/or rib fracture after lung SBRT.	The median interval to the onset of severe pain and/or fracture was 7.1 months. The risk of CW toxicity was fitted to the median effective concentration dose-response model. The CW volume receiving 30 Gy best predicted the risk of severe CW pain and/or rib fracture (R(2) = 0.9552). A volume threshold of 30 cm(3) was observed before severe pain and/or rib fracture was reported. A 30% risk of developing severe CW toxicity correlated with a CW volume of 35 cm(3) receiving 30 Gy. The development of CW toxicity is clinically relevant, and the CW should be considered an organ at risk in treatment planning. The CW volume receiving 30 Gy in 3-5 fractions should be limited to <30 cm(3), if possible, to reduce the risk of toxicity without compromising tumor coverage.	2

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
69. Pettersson N, Nyman J, Johansson KA. Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy of non-small cell lung cancer: a dose- and volume-response analysis. *Radiother Oncol* 2009; 91(3):360-368.	Observational-Tx	68 patients	To analyze the dose-response and the volume-response of radiation-induced rib fractures after hypofractionated SBRT.	It was possible to quantify the risk of radiation-induced rib fracture using response curves and information contained in the dose-volume histograms. Absolute volumes provided better fits than relative volumes and dose-response curves were more suitable than volume-response curves. For the dose given by the 2 cm(3) cut-off volume, D(2 cm(3)), the logistic dose-response curve for three fractions was parameterized by D(50)=49.8 Gy and gamma(50)=2.05. Consequently, for a median follow-up of 29 months, if D(2 cm(3))<3 x 7.0 Gy the risk is close to 0, and the 5% and 50% risks are given by D(2 cm(3))=3 x 9.1 Gy and 3 x 16.6 Gy, respectively. In this group of patients, the risk for radiation-induced rib fracture following hypofractionated SBRT was related to the dose to 2 cm(3) of the rib.	2
70. Mutter RW, Liu F, Abreu A, Yorke E, Jackson A, Rosenzweig KE. Dose-volume parameters predict for the development of chest wall pain after stereotactic body radiation for lung cancer. *Int J Radiat Oncol Biol Phys* 2012; 82(5):1783-1790.	Observational-Tx	126 patients	To examine the dose-volume histogram of the CW for these patients to determine predictors of Grade ≥2 CW pain.	With a median follow-up of 16 months, the 2-year estimated actuarial incidence of Grade ≥2 CW pain was 39%. The median time to onset of Grade ≥2 CW pain (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0) was 9 months. There was no predictive advantage for biologically corrected dose over physical dose. Neither fraction number (P=0.07) nor prescription dose (P=0.07) were significantly correlated with the development of Grade ≥2 CW pain. Cox Proportional Hazards analysis identified significant correlation with a broad range of dose-volume combinations, with the CW volume receiving 30 Gy (V30) as one of the strongest predictors (P<0.001). CW2cm consistently enabled better prediction of CW toxicity. When a physical dose of 30 Gy was received by more than 70 cm(3) of CW2cm, there was a significant correlation with Grade ≥2 CW pain (P=0.004).	2

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
71. Ambrogi MC, Lucchi M, Dini P, et al. Percutaneous radiofrequency ablation of lung tumours: results in the mid-term. *Eur J Cardiothorac Surg* 2006; 30(1):177-183.	Observational-Tx	79 RFA, performed to treat 64 lesions in 54 patients	To evaluate RFA of lung tumors.	In all cases, except two, the procedure was technically successful. Morbidity consisted in 10 cases (12.7%) of partial pneumothorax, 1 haematoma of the CW and 1 pleural effusion. At a mean follow-up of 23.7 months (range of 6-50) we recorded a 61.9% of complete responses, with a higher rate in the metastatic lesions (70.8%) and in those <3 cm (69.7%). Mean (median) OS and local progression-free interval were 17.3 (28.9) months and 12.9 (24.1) months, respectively. Efficacy of RFA in the mid-term seems to settle at a promising level, with better results for metastatic lesions and, above all, for lesions smaller than 3 cm. Notwithstanding these encouraging results, RFA remains an alternative local therapy only when surgery cannot be performed, especially in NSCLC.	2
72. de Baere T, Palussiere J, Auperin A, et al. Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation. *Radiology* 2006; 240(2):587-596.	Observational-Tx	60 patients with 100 lung tumors	To prospectively evaluate the local efficacy of RFA of lung neoplasms, with a minimum follow-up period of 1 year.	97/100 targeted tumors were treated and required 163 RFAs (1.68 per tumor), each lasting 14 minutes +/- 8, delivered during 74 procedures. The 18-month estimated rate of incomplete local treatment at CT was 7% (95% CI: 3%, 14%) per tumor and 12% (95% CI: 5%, 23%) per patient. An ablation area at least four times larger than the initial tumor was predictive of complete ablation treatment (P=.02). There was a trend toward better efficacy for tumors <2 cm in diameter (P=.066). OS and lung DFS at 18 months were 71% and 34%, respectively. The main adverse event was a pneumothorax, which occurred in 54% of procedures, but a chest tube was required in only 9% of the procedures. No modification of respiratory function was found when spirometry measurements obtained before and within 2 months after RFA were compared (P=.51). RFA has a high local efficacy and is well tolerated.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
73. Fernando HC, De Hoyos A, Landreneau RJ, et al. Radiofrequency ablation for the treatment of non-small cell lung cancer in marginal surgical candidates. *J Thorac Cardiovasc Surg* 2005; 129(3):639-644.	Observational-Tx	21 tumors in 18 patients	To report an initial experience with RFA for peripheral, primary NSCLC as option for patients with NSCLC who are not surgical candidates or who refuse operation.	One postoperative death occurred from pneumonia after open RFA. Median hospital stay was 2.5 days. A chest tube or pigtail catheter was required in 7 patients (38.9%) for procedure-related pneumothoraces. At a median follow-up of 14 months, 15 patients (83.3%) were alive. Local progression occurred in 8 nodules (38.1%). Mean and median progression-free intervals were 16.8 and 18 months, respectively. For stage I cancers, mean progression-free interval was 17.6 months. Median progression-free interval was not reached. This study demonstrates the feasibility of RFA for small, peripheral NSCLC tumors. Local control is comparable to, if not better than, that provided by RT. RFA should continue to be evaluated by thoracic surgeons as a noninvasive therapy for the high-risk patient with NSCLC.	2

Early Stage Non-Small-Cell Lung Cancer
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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
74. Lagana D, Carrafiello G, Mangini M, et al. Radiofrequency ablation of primary and metastatic lung tumors: preliminary experience with a single center device. *Surg Endosc* 2006; 20(8):1262-1267.	Review/Other-Tx	15 patients	To assess the feasibility and short-term results for percutaneous RFA in the treatment of primary and secondary lung tumors.	In terms of complications, there were 5 cases of pneumothorax (2 resolved spontaneously and 3 were drained through a coaxial needle), 4 middle pleural reactions, and one hemothorax that required draining surgically. Follow-up evaluation was performed for 16/18 lesions. Stability was observed in one of two central tumors that received partial ablation. The remaining 15 tumors that received a complete ablation were followed up for a mean of 5 months (range, 1-12 months). All 15 lesions appeared to be hypodense at the CT examination. Dimension reduction with progressive fibrotic scar formation was observed in seven of seven lesions during a follow-up period of 6 months or more. A recurrence at the site of the treatment for two of three lesions was observed during a 12-month follow-up period. One of these received a second RFA. Five patients experienced systemic disease progression. In four of these five patients, this progression was not associated with recurrence at the site of the treatment. RFA seems to be possible for "nonsurgical" patients with primary and secondary lung tumors. Good results in terms of local tumor control were observed during short-term follow-up evaluation.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
75. Nguyen CL, Scott WJ, Goldberg M. Radiofrequency ablation of lung malignancies. *Ann Thorac Surg* 2006; 82(1):365-371.	Review/Other-Tx	N/A	To address issues and provides the thoracic surgeon with a current review of the application of RFA to lung tumors.	While the indications for RFA and other image-guided therapies for lung cancer may currently be limited to patients who are "medically inoperable," the experiences of vascular and cardiac surgeons suggest that indications for the use of emerging technologies expand over time. Thoracic surgeons are and should remain the experts in the treatment of patients with early-stage lung cancer. Thoracic surgery professional societies should be active and not reactive, formulating policies that will enable us to incorporate RFA and other emerging technologies into our practices for the safety and well-being of our patients.	4

Evidence Table Key

Study Quality Category Definitions

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

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

BED = Biologically effective dose

CI = Confidence interval

CT = Computed tomography

CTV = Clinical target volume

CW = Chest wall

DFS = Disease-free survival

FEV1= Forced expiratory volume in one second

HR = Hazard ratio

NSCLC = Non-small-cell lung cancer

OS = Overall survival

PET = Positron emission tomography

PORT = Postoperative radiotherapy

PTV = Planning target volume

RFA = Radiofrequency ablation

RT = Radiation therapy

SBRT = Stereotactic body radiation therapy

SUV = Standardized uptake value

VATS = Video-assisted thoracic surgery