

TREATMENT OPTIONS FOR STAGE I/II NON-SMALL CELL LUNG CANCER

The American Cancer Society projected 221,200 new cases of lung cancer and 158,040 deaths from the disease in the United States in 2015. Most deaths occur in patients with Stage III/IV disease. For decades Surgery has been the preferred method for curative treatment of Stage I/II Non-Small Cell Lung Cancer. External Radiation Therapy (XRT) doses were limited because of factors such as primitive treatment planning systems, limited shielding capability, and lack of energy modulation. The standard XRT dose was 6000 cGy in 30 fractions. Modern day radiation treatment systems have allowed marked escalation of XRT doses to the range of 8000 to 10,000 cGy with reduction in normal lung exposure. This can be done in a number of ways, including Stereotactic Body Radiation Therapy (SBRT), Intensity Modulated Radiation Therapy (IMRT), and 3-Dimensional Conformal Radiation Therapy (3-D CRT). SBRT has also been called Stereotactic Ablative Radiotherapy (SABR). Data on these technologies has been accumulating since 2002. The results have compared favorably to Surgery, both with regard to cure and complications. SBRT delivers XRT doses in far fewer treatments, which results in a much higher equivalent radiation dose, e.g. 10,000 cGy. The following SBRT/SABR data are representative of the medical literature :

STAGE I/II NSCLC RESULTS WITH HIGH DOSE SBRT/SABR

<u>STUDY</u>	<u>#PTS</u>	<u>Gy</u> <u>DOSE</u>	<u>Fx</u>	<u>SURV.</u>	<u>F/U</u>	<u>COMPLICATIONS</u>	
Xia ¹	43	50	10	77%	3 yrs	2%	
Hof ²	42	19-30	1	37%	3 yrs	2%	
Fakiris ³	70	60-66	3	43%	3 yrs	14%	
Takeda ⁴	63	50	5	76%	3 yrs	5%	
Ricardi ⁵	196	48-60	3-8	68%	3 yrs	nr	
Grills ⁶	505	54	3	60%	2 yrs	10%	
Guckenberger ⁷	582	54		3	47%	2 yrs	7%
Shibamoto ⁸	180	44-52	4	52%	5 yrs	13-21%	
Onishi ⁹	87	45-72	3-10	67%	5 yrs	1%	
Timmerman ¹⁰	59	54	3	56%	3 yrs	16%	
Stephans ¹¹	94	50-60	3-5	80%	1.5 yrs	2%	
Van der Voort ¹²	70	45-60	3	62%	2 yrs	13%	
Uematsu ¹³	50	50-60	5-10	66%	3 yrs	0%	
Zimmerman ¹⁴	68	24-40	3-5	53%	3 yrs	4%	
Taremi ¹⁵	108	50-60	3-10	77%	4 yrs	0%	
Baumann ¹⁶	138	30-48	2-4	26%	5 yrs	10%	
Davis ¹⁷	723	10-80	1-5	50%	2.5 yrs	nr	
Koshy ¹⁸	498	45-60	3-4	50%	3 yrs	nr	
Rosen ¹⁹	79	48-60	4-5	58%	3 yrs	0%	
Jeppesen ²⁰	100	45-66	3	50%	3 yrs	nr	
Chang ²¹	130	50	4	50%	5 yrs	2.3%	
Senthi ²²	676	54-60	3-8	57%	5 yrs	nr	
Lagerwaard ²³	382	60	3-8	50%	3.5 yrs	nr	
Hiraoka ²⁴	241	48	4	44%	5 yrs	nr	
Chang@ ²⁵	58	50	5	95% (SBRT)	3 yrs	10%	
				79% (Surgery)	3 yrs	48%	
				p < 0.05		p < 0.05	

*Cause specific survival
@Randomized Trial

Most of this work has been pioneered in Europe and Japan. The last study in the table above by Chang et al, (Lancet, 2015) is the 1st randomized trial to compare SBRT/SABR to the historical standard of Surgery. The randomized trial is the gold standard in medicine to judge results with different treatments. SBRT/SABR proved superior to Surgery in regard to survival. Complications were also markedly less. In the SBRT/SABR group, 10% patients had grade 3 complications, which included chest wall pain, cough, shortness of breath, fatigue, and one case of rib fracture. There were no grade 4 (death) complications. In the Surgery group, 48% of patients experienced grade 3 or 4 complications, including 4% deaths. SBRT/SABR in contrast to surgery, is a painless non-invasive procedure, done entirely as an outpatient in 5 days. Each treatment takes about 30 minutes to deliver.

These results compare very favorable to modern day surgical sleeve lobectomy for clinical Stage I/II NSCLC. The following data are representative of the medical literature :

STAGE I/II NSCLC
RESULTS WITH SURGICAL SLEEVE LOBECTOMY

<u>AUTHOR</u>	<u>#PTS</u>	<u>SURVIVAL</u>	<u>F/U</u>	<u>OPERATIVE MORTALITY</u>
Park ²⁶	157	58.4%	5 yrs	1.0%
Van Schil ²⁷	145	49%	5 yrs	4.8%
Rea ²⁸	199	39.7%	5 yrs	4.5%
De Leyn ²⁹	77	45.6%	5 yrs	3.9%
Ludwig ³⁰	116	39%	5 yrs	4.3%
Merritt ³¹	196	44%	5 yrs	2.0%
Tronc ³²	184	52%	5 yrs	1.6%
Fadel ³³	169	52%	5 yrs	2.9%
Yildizeli ³⁴	218	53%	5 yrs	4.1%
Deslauriers ³⁵	184	52%	5 yrs	1.6%
Martini ³⁶	511*	75%	5 yrs	2.3%

*All Stage I NSCLC

Radiation Oncologists of Central Arizona (ROCA) has the state of the art delivery system for SBRT/SABR, Cyberknife. In addition, Dr. John Kresl, a co-author on the landmark randomized trial paper discussed above, is the Medical Director of the Phoenix Cyberknife Center. He is a leading pioneer in the field of SBRT/SABR.

References :

1. Xia T, et al. Promising Clinical Outcome of Stereotactic Body Radiation Therapy for Patients with Inoperable Stage I/II Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys, 2006 ; 66[1]:117.
2. Hof H, et al. Stereotactic Single Dose Radiotherapy (Radiosurgery) of Early Stage Non-Small Cell Lung Cancer. Cancer, 2007 ; 110[1]:148.
3. Fakiris AJ, et al. Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer : Four Year Results of a Prospective Phase II Study. Int J Radiat Oncol Biol Phys, 2009 ; 75[3]:677.
4. Takeda A, et al. Stereotactic Body Radiation Therapy for Primary Lung Cancer at a Dose of 50 Gy Total in 5 Fractions to the Periphery of the Planning Target Volume Using a Superposition Algorithm. Int J Radiat Oncol Biol Phys, 2009 ; 73 [2] : 442.
5. Ricardi U, et al. Stereotactic Body Radiation Therapy for Stage I Histologically Proven Non-Small Cell Lung Cancer : An Italian Multi-Center Observational Study. Lung

- Cancer, 2014 ; 84[3] :248.
6. Grills IS, et al. A Collaborative Analysis of Stereotactic Body Radiation Therapy Outcomes for Early Stage Non-Small Cell Lung Cancer Using Daily On-Line Cone Beam CT Image Guide Radiation Therapy. *J Thorac Oncol*, 2012 ; 7[9]:1382.
 7. Guckenberger M, et al. Safety and Efficacy of Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer in Routine Clinical Practice : A Patterns of Care and Outcome Analysis. *J Thorac Oncol*, 2013 ; 8[8]:1050.
 8. Shibamoto Y, et al. Stereotactic Body Radiation Therapy Using a Radiology Based Regimen for Stage I Non-Small Cell Lung Cancer : Five Year Mature Results. *J Thorac Oncol*, 2015 ; 10[6]:960.
 9. Onishi H, et al. Stereotactic Body Radiation Therapy for Operable Stage I Non-Small Cell Lung Cancer : Can Stereotactic Body Radiation Therapy be Comparable to Surgery? *Int J Radiat Oncol Biol Phys*, 2011 ; 81[5]:1352.
 10. Timmerman R, et al. Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer. *JAMA*, 2010 ; 303[11]:1070.
 11. Stephens KL, et al. A Comparison of Two Stereotactic Body Fractionation Schedules for Medically Inoperable Stage I Non-Small Cell Lung Cancer. The Cleveland Clinic Experience. *J Thorac Oncol*, 2009 ; 4[8]:976.
 12. Van der Voort van Zyp NC, et al. Stereotactic Radiotherapy with Real-Time Tumor Tracking for Non-Small Cell Lung Cancer : Clinical Outcome. *Radiother Oncol*, 2009 ; 91[3]:296.
 13. Uematsu M, et al. CT Guided Frameless Stereotactic Radiotherapy for Stage I Non-Small Cell Lung Cancer : A Five Year Experience. *Int J Radiat Oncol Biol Phys*, 2001 ; 51[3]:666.
 14. Zimmerman FB, et al. Stereotactic Hypofractionated Radiotherapy in Stage I (T1-2,N0,M0) Non-Small Cell Lung Cancer. *Acta Oncol*, 2006 ; 45[7]:796.
 15. Taremi M, et al. Stereotactic Body Radiation Therapy for Medically Inoperable Lung Cancer : Prospective Single Center Study of 108 Consecutive Patients. *Int J Radiat Oncol Biol Phys*, 2012 ; 82[2]:967.
 16. Baumann P, et al. Factors Important for Efficacy of Stereotactic Body Radiation Therapy for Medically Inoperable Stage I Lung Cancer : A Retrospective Analysis of Patients Treated in the Nordic Countries. *Acta Oncol*, 2006 ; 45[7]:787.
 17. Davis JN, et al. Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer : Clinical Outcomes from a National Patient Registry. *J Radiat Oncol*, 2015 ; 4[1]:55.
 18. Koshy M, et al. Increasing Radiotherapy Dose is Associated with Improve Survival in Patients undergoing Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys*, 2015 ; 91[2]:344.
 19. Rosen JR, et. Helical Image Guided Stereotactic Body Radiation Therapy for the Treatment of Early Stage Lung Cancer : A Single Institution Experience at the Willis-Knighton Cancer Center. *Tumori*, 2014 ; 100[1]:42.
 20. Jeppesen SS, et al. Stereotactic Body Radiation Therapy vs. Conventional Radiation Therapy in patient with Early Stage Non-Small Cell Lung Cancer : An Updated Retrospective Study on Local Failure and Survival Rates. *Acta Oncol*, 2013 ; 52[7]:1552.
 21. Chang JY, et al. Clinical Outcome and Predictors of Survival and Pneumonitis after Stereotactic Ablative Radiation Therapy for Stage I Non-Small Cell Lung Cancer. *Radiat Oncol*, 2012 ; 10[7]:152.
 22. Senthil S, et al. Patterns of Disease Recurrence after Stereotactic Ablative Radiation Therapy for Early Stage Non-Small Cell Lung Cancer : A Retrospective Analysis. *Lancet Oncol*, 2012 ; 13[8]:802.
 23. Lagerwaard FJ, et al. Patient Reported Quality of Life after Stereotactic Ablative

- Radiation Therapy for Early Stage Lung Cancer. *J Thorac Oncol*, 2012 ; 7[7]:1148.
24. Hiraoka M, et al. Stereotactic Body Radiation Therapy for Early Stage Lung Cancer. *Cancer Radiother*, 2007 ; 11[1]:32.
 25. Chang JY, et al. Stereotactic Body Radiation Therapy vs. Lobectomy for Operable Stage I Non-Small Cell Lung Cancer : A Pooled Analysis of Two Randomized Trials. *Lancet Oncol*, 2015 ; 16[6]:630.
 26. Park JS, et al. Sleeve Lobectomy as an Alternative Procedure to Pneumonectomy for Non-Small Cell Lung Cancer. *J Thorac Oncol*, 2010 ; 5[4]:517.
 27. Van Schill PE, et al. TNM Staging and Long-Term Follow-up After Sleeve Resection for Bronchogenic Tumors. *Ann Thorac Surg*, 1991 ; 52[5]:1096.
 28. Rea F, et al. A Quarter of a Century Experience with Sleeve Lobectomy for Non-Small Cell Lung Cancer. *Eur J Cardiothorac Surg*, 2008; 34[3]:488.
 29. De Leyn P, et al. Sleeve Lobectomy for Non-Small Cell Lung Cancer. *Acta Chir Belg*, 2003 ; 103[6]:570.
 30. Ludwig C, et al .Comparison of Morbidity, 30 day Mortality, and Long-Term Survival after Pneumonectomy and Sleeve Resection for Non-Small Cell Lung Cancer. *Ann Thorac Surg*, 2005 ; 79[3]:968.
 31. Merritt RE, et al. Long-Term Results of Sleeve Lobectomy in the Management of Non-Small Cell Lung Cancer and Low Grade Neoplasms. *Ann Thorac Surg*, 2009 ; 88[5] : 1574.
 32. Tronc F, et al. Long-Term Results of Sleeve Lobectomy for Lung Cancer. *Eur J Cardiothorac Surg*, 2000 ; 17[5]:550.
 33. Fadel E, et al. Sleeve Lobectomy for Bronchogenic Carcinomas : Factors Affecting Survival. *Ann Thorac Surg*, 2002 ; 74[3]:851.
 34. Yildizeli B, et al. Morbidity, Mortality, and Long-Term Survival After Sleeve Lobectomy for Non-Small Cell Lung Cancer. *Eur J Cardiothorac Surg*, 2007 ; 31[1]:95.
 35. Deslauriers J, et al. Sleeve Lobectomy vs. Pneumonectomy for Lung Cancer : A Comparative Analysis of Survival and Sites of Recurrences. *Ann Thorac Surg*, 2004; 77[4]:1152.
 36. Martini N, et al. Incidence of Local Recurrence and Second Primary Tumors in Resected Stage I Lung Cancer. *J Thorac Cardiovasc Surg*, 1995 ; 109[1]:120.