

Surgery has historically been considered the only hope for a cure of lung cancer since 1933, when Dr. Evarts Graham performed the first successful pneumonectomy for lung cancer. The idea was to resect tumor and adjacent lymph nodes plus a generous surgical margin. Soon thereafter, surgery (lobectomy or pneumonectomy with lymph node dissection or sampling) became the standard treatment for patients with localized disease who were physically able to tolerate the operation. However, surgical resection is associated with significant morbidity and mortality; an analysis of a nationwide inpatient sample database indicated that about 45% patients who undergo surgery develop severe postoperative complications (1). Surgical mortality rates have ranged from 1.8% to 3.8% at 30 days and 4% to 6.5% at 90 days. Even for patients with stage I lung cancer, 5-year overall survival rates after surgery range from 60% to 80%; roughly 5% to 10% patients experience recurrence in the hilar or mediastinal lymph nodes, and another 10% to 20% develop distant metastasis even though the mediastinal lymph nodes had been sampled or dissected (2). Clearly, there is room for improvement.

With the wide use of lung cancer screening programs, more early-stage lung cancers are anticipated to be detected. The median age of patients with lung cancer is 70 years at diagnosis ([http://seer.cancer.gov/csr/1975\\_2012](http://seer.cancer.gov/csr/1975_2012)). Many such patients will have comorbid conditions such as chronic obstructive pulmonary disease (COPD), cardiovascular disease, diabetes and others. Thus it remains crucial to develop curative treatment that has minimal side effects. The recently invented technique of video-assisted thoracoscopy lobectomy (VATS) seems to reduce the rate of severe postoperative complications somewhat, from 45% to 41%, but has not changed operative mortality rates relative to open thoracotomy (1). Lymph node sampling or dissection seems to be compromised in some cases, but overall survival rates remain similar for patients treated with either approach.

Technologic innovations allowing the implementation of image-guided stereotactic ablative radiotherapy (SABR, also called stereotactic body radiation therapy, SBRT) have enabled radiation oncologists to deliver tightly focused, high biologically effective doses of radiation (>100 to 130 Gy), enough to kill nearly all cancer cells within the target, to early-stage lung cancers; SABR has produced local control rates in excess of 95%. With the use of modern-day disease staging procedures such as computed tomography (CT), positron emission tomography (PET)/CT, and endobronchial ultrasonography (EBUS), rates of lymph node recurrence and distant failure after SABR for stage I NSCLC are 5%–13% and 15%–20% (3), rates that are similar to those after surgical resection even though elective lymph node irradiation is not given. SABR has become the standard of care for medically inoperable stage I NSCLC (4), and its implementation has improved national lung cancer survival rates (5).

Nevertheless, the question remains: which is better for operable stage I NSCLC, surgery or SABR? Most propensity-matched retrospective studies have shown the two modalities to produce similar overall survival rates (6), and only a few studies have indicated a survival advantage for surgery. However, retrospective comparisons inherently have selection bias, and so the best approach is to conduct randomized studies. Unfortunately, all of the randomized studies that have been attempted to date, that is, the STereotActic Radiotherapy *vs.* Surgery (STARS) trial, the Radiosurgery Or Surgery for Early Lung cancer (ROSEL) trial, and the ACOSOG Z4099/RTOG 1021 trial, “A Randomized Phase III Study of Sublobar Resection (+/- Brachytherapy) versus Stereotactic Body Radiation Therapy in High Risk Patients with Stage I Non-Small Cell Lung Cancer (NSCLC),” were closed prematurely because of poor enrollment, chiefly because the treating physicians tended to favor surgery. Pooled analysis of the STARS and ROSEL trials showed that SABR produced better overall survival and similar progression-free survival (7). The authors of that analysis concluded that “SABR has emerged as a noninvasive standard treatment alternative to surgery for elderly patients and for patients with clinically significant comorbidities and should be considered as an option for treatment of operable stage I NSCLC.” These studies, and this analysis, have triggered significant debate in the thoracic oncology community. The significance and limitations have been widely discussed, and newer randomized studies have been opened for enrollment in the United States [Veterans Affairs Lung cancer surgery Or stereotactic Radiotherapy (VALOR)]; Sublobar Resection (SR) versus Stereotactic Ablative Radiotherapy (SAbR) in High Risk Patients with Stage I NSCLC (STABLE-MATES), Europe [Stereotactic Ablative Radiotherapy *vs.* surgery in patients with peripheral stage I non-small cell lung cancer considered higher risk of complications from surgical resection (SABRTOOTH)], and China [Radical Resection *vs.* Ablative Stereotactic Radiotherapy in Patients With Operable Stage I NSCLC (POSTILV)].

Interestingly, preliminary findings support the supposition that SABR can not only kill cancer cells but also release tumor-associated antigens, which can function as a cancer-specific “vaccine” in situ that can fight local, regional, and distant recurrence. Combinations of SABR with immunotherapies such as checkpoint inhibitors (“iSABR”) could significantly

improve treatment efficacy and cure rates (8). Undoubtedly these and other combinations of technologic and biologic advances will lead to fundamental changes in the way we treat lung cancer.

This book provides a comprehensive review of SABR and its use for medically inoperable or operable early-stage lung cancer or for oligometastases lung cancer. Until now, the question of which treatment is optimal for medically operable stage I lung cancer—surgery or SABR?—remains controversial. Certainly additional randomized studies are needed. This topic should not represent a battleground between thoracic surgeons and radiation oncologists. Rather, attention should be directed toward the battle our patients are fighting. Lung cancer is still the number 1 cancer killer in the world. No one, neither patients nor physicians (including surgeons and radiation oncologists), is satisfied with the status quo for lung cancer outcomes. Discoveries in the evolution of technology and biology are providing unique opportunities to expand our understanding of lung cancer and how to eliminate it. As Dr. Graham once said, “*Perhaps in the future some non-surgical method will be discovered which will be not only more simple in its execution but more reliable in its results than a surgery.*” It is quite possible that certain patients will benefit more from surgery, and others will benefit more from SABR. It is our job as physicians to identify which patients belong to which group, so that we can provide truly individualized care.

## References

1. Paul S, Sedrakyan A, Chiu YL, et al. Outcomes after lobectomy using thoracoscopy vs thoracotomy: a comparative effectiveness analysis utilizing the Nationwide Inpatient Sample database. *Eur J Cardiothorac Surg* 2012;43:813-7.
2. Lou F, Huang J, Sima CS, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. *J Thorac Cardiovasc Surg* 2013;145:75-81.
3. Senthil S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012;13:802-9.
4. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA* 2010;303:1070-6.
5. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 2010;28:5153-9.
6. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. *JAMA Surg* 2014;149:1244-53.
7. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;16:630-7.
8. Bernstein MB, Krishnan S, Hodge JW, et al. Immunotherapy and stereotactic ablative radiotherapy (ISABR): a curative approach? *Nat Rev Clin Oncol* 2016. [Epub ahead of print].

**Joe Y. Chang, Professor, Director**  
*Stereotactic Ablative Radiotherapy,*  
*MD Anderson Cancer Center*