# Additional data in the debate on stage I non-small cell lung cancer: surgery versus stereotactic ablative radiotherapy

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**Abstract:** Lobectomy has been the standard of care for patients with early stage non-small cell lung cancer (NSCLC), resulting in nearly universal local control and excellent overall survival. However, up to one-quarter of early stage patients are unable to undergo or refuse definitive resection. With the increasing adoption of stereotactic ablative radiotherapy (SABR) over conventionally fractionated radiotherapy among medical inoperable patients, tumor control and overall survival rates in this population have significantly improved. Trials demonstrating excellent outcomes among both medically inoperable and medical operable patients with stage I NSCLC have spurred interest in comparisons between surgery and SABR. The recent publication of the randomized STARS and ROSEL trials demonstrated fewer toxicities and an improvement in overall survival among patients treated with SABR compared with surgery. Based on these trials and retrospective comparisons between the modalities, definitive SABR now more firmly appears to be a viable first-line option for treating patients with operable stage I NSCLC.

**Keywords:** Lobectomy; lung cancer; randomized; stereotactic ablative radiotherapy (SABR); stereotactic body radiation therapy (SBRT)

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## Introduction

More than 1.8 million people are estimated to be diagnosed worldwide with lung and bronchus cancers annually. Despite improvements in therapies and increased efforts towards smoking cessation, lung cancer continues to be the greatest cause of mortality from cancer, with an estimated 1.6 million deaths expected globally each year (1). Non-small cell lung cancer (NSCLC) accounts for approximately 87% of new lung cancer diagnoses, and approximately 15% of patients with NSCLC have localized diseased confined to their primary tumor site at the time of diagnosis (2,3). Additionally, the incidence of early stage NSCLC is expected to continue to rise with the increasing life expectancy in elderly patients, advances in medical imaging, implementation of low-dose computed tomography lung cancer screening programs based on the findings of the National Lung Screening Trial (4,5), and increasing investigation into circulating tumor products and other potential methods of early NSCLC detection (6).

## Surgery-based standard of care

Surgery has been long established to be the preferred treatment option for patients with early stage NSCLC, particularly those with tumors ≤5 cm in size without local invasion (7,8). Based on available literature, the American College of Chest Physicians Evidence-based Clinical Practice Guidelines in 2007 determined that "surgical resection remains the treatment of choice for stage I and II NSCLC" (8). Lobectomy or greater anatomical resection has consistently been reported to achieve local control rates of >90% for stage I NSCLC and generally is the preferred surgical approach over sublobar resections with wedge resection or segmentectomy (8,9). In patients able

to tolerate operative interventions but thought not to be able to undergo a lobar resection, those clinical practice guidelines recommend sublobar resection over nonsurgical intervention such as radiation therapy (8) or other ablative techniques (10).

Although surgery is the most oncologic way to treat early stage NSCLC, resection does have several limitations. First, at least 15-20% of patients diagnosed with stage I NSCLC are unable to undergo or refuse definitive surgical resection (11,12). Second, complication rates following surgery are not trivial, especially among older patients and those with higher comorbidity index scores. In fact, a recent National Cancer Data Base study assessing 124,418 major lung resections from 2007 to 2011 found a 30-day mortality rate of 2.8% and 90-day mortality rate of 5.4% (13). Furthermore, although lobectomy is considered the standard-of-care surgical procedure for stage I NSCLC, 5-15% of patients require a bilobectomy and another 4-15% require a pneumonectomy (14), which are known to increase the risk of perioperative mortality compared with lobectomy (13).

## Advent of stereotactic body radiotherapy

For patients who are medically inoperable, radiotherapy delivered with conventional fractionation, typically in 1.8-2.0 Gy daily fractions, has been employed as standard therapy but was generally reserved for patients of borderline resectability, who were medically-inoperable with cardiovascular or chronic pulmonary diseases, or who refused surgery (8,15,16). Therefore, patients with stage I NSCLC treated with definitive radiotherapy have generally been older with higher medical comorbidity scores and higher rates of intercurrent non-cancer mortality than patients undergoing surgery. As a result, the reported 5-year survival and local control rates after conventionally fractionated radiotherapy of 17-55% and 40-70%, respectively, have been far inferior to the rates of 50-80% and 80-95% with anatomical surgical resection (17).

Dose escalation and altered fractionation regimens were investigated to attempt to improve the poor local control rates seen after conventionally fractionated radiotherapy. Early reports using hypofractionation (fraction sizes greater than standard 1.8-2.0 Gy fractions) to smaller radiotherapy fields without prophylactic irradiation to nodal regions at risk of developing metastasis demonstrated improved local control and overall survival compared with conventionally fractionated radiotherapy (18,19). Based on these findings and the successful applications of high dose stereotactic radiosurgery for primary and metastatic brain tumors, high dose stereotactic treatments were investigated. Early clinical applications of this approach to treat early stage NSCLC, termed stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR), began in the late 1990's.

SABR involves the administration of ulta-high dose, ablative fractions of radiation to a target, which allows for maximizing cell-killing effect of tumor thought to be from the delivery of higher biological equivalent doses of radiotherapy than can be achieved with conventional fractionation. In contrast to conventional irradiation, which is delivered daily for six to eight weeks, SABR is typically administered in one to give fractions in doses of 6-34 Gy per fraction. Through a rapid dose falloff gradient that compasses the tumor, SABR can also minimize irradiation received by surrounding normal organs (17,20,21). SABR requires accurate delineation of the tumor and accurate and reproducible localization of the target lesion relative to a known three dimensional reference system, generally with image-guided radiotherapy used to verify patient positioning and tumor localization before to each fraction (22,23).

Across prospective and retrospective studies, SABR results in local control rates of 80-100% and overall survival rates of 40-80% at 3 years in medically inoperable patients (17). An early phase II study of 70 patients treated with SBRT to 60-66 Gy in 3 fractions found the local control to be 95% and overall survival to be 55% at 2-years (24). The first multi-centered cooperative group phase II trial [Radiation Therapy Oncology Group (RTOG) 0236] found a 3-year primary tumor local control rate of 97.6%, local-regional control rate of 87.2%, and overall survival rate of 55.8% among 55 patients with stage I NSCLC treated in three fractions with SBRT to 54 Gy (25).

These excellent outcomes among medically inoperable patients have spurred interest in investigating SABR in potentially operable patients with stage I NSCLC (26,27). In a study of 87 patients with stage I NSCLC who were medically operable but refused surgery, treatment with SABR to 45-72.5 Gy in 3-10 fractions was associated with a 5-year cumulative local control rate of 92% for T1 tumors and 73% for T2 tumors, with overall survival rates of 72% for stage IA and 62% for IB, which are comparable to outcomes reported in surgical series (28).

Mature data from completed phase II trials of SBRT in medically-operable patients are pending. In an interim analysis of Japan Clinical Oncology Group (JCOG 0403), 65 patients with medically operable cT1N0M0 NSCLC

 

were treated with SABR in 4 fractions to 48 Gy. At a median follow-up of 45.4 months, the overall survival was 76.0%, progression-free survival was 54.5%, and local-progression free survival was 68.5% at 3 years. Toxicity was limited to grade 3 chest pain (1.5%), dyspnea (3.1%), hypoxia (1.5%), and pneumonitis (3.1%), without any grade 4 or 5 toxicities observed (29). In an interim analysis of RTOG 0618, 26 evaluable patients with cT1-T2N0M0 NSCLC were treated in three fractions to 54 Gy. At a median follow-up of 25 months, the overall survival was 84.4%, progression-free survival was 65.4%, primary tumor failure was 7.7%, regional failure was 11.7%, and distant failure was 15.4% at 2 years. Sixteen percent had grade 3 toxicities, while no grade 4-5 toxicities were observed (30).

Across studies, SABR has generally been shown to be well tolerated. Acute SABR complications, including fatigue, skin erythema, mild hematologic suppression and cough, are typically mild and transient and occur in 5-40% of patients (26). Subacute and late toxicities are less common but potentially more severe and can include radiation pneumonitis, chronic dyspnea, hemoptysis, chest wall pain, rib fracture, bronchial stenosis or necrosis, esophageal injury, and brachial plexopathy (17). High grade morbidity and even mortality has been reported with SABR delivered to centrally located tumors within 2 cm of the proximal bronchial tree (26), although treatment of central tumors with SABR can be effective and appears safer when delivered in regimens of greater than three fractions (31).

## Surgery versus SABR

Given the efficacy of SABR reported in both medically inoperable and operable patients with stage I NSCLC, there has been much interest in comparing SABR with surgical resection. However, direct comparisons from retrospective and population-based studies have been faced with challenges. Patients who have undergone SABR have generally been older and had higher comorbidity index scores than those undergoing surgery, potentially biasing survival comparisons in favor of surgery. Additionally, differences exist in how some studies have defined local failure. Surgical series have define local failure variably as recurrence within the same lobe, another lobe of the ipsilateral lung, or regional lymph nodes, whereas many SABR series have defined local failure as progression at the site of the primary tumor or within the high dose treatment region, potentially biasing local control comparisons in favor of SABR.

Furthermore, patients treated with SABR have generally received less extensive or less invasive lymph nodal staging compared with patients undergoing definitive surgical therapy who generally undergo a lymph node dissection at the time of primary tumor resection. Up to one-third of patients treated with SABR for presumed stage I NSCLC might actually have more advanced disease and nodal metastasis (32), potentially biasing survival comparisons in favor of surgery. This is not a trivial point given that data from over 18,000 patients analyzed as part of the IASLC Lung Cancer Staging Project demonstrated a dramatic reduction in overall survival based on clinical stage when compared to surgical stage (33).

Despite these and other limitations, some existing comparisons between the modalities are noteworthy. In an early retrospective comparison of 124 patients with stage I NSCLC who were ineligible for lobectomy treated with SABR (n=58) or wedge resection (n=69) at William Beaumont Hospital, SBRT patients were found to be older and have higher comorbidity scores. However, SBRT was associated fewer local recurrences (5% *vs.* 24%, P=0.05) and locoregional recurrences (5% *vs.* 29%, P=0.03). There was no difference in cause-specific survival (93% *vs.* 94%, P=0.53), but SBRT patients had an inferior overall survival (72% *vs.* 87%, P=0.01) most consistent with pre-treatment differences between patients receiving each modality (34).

In another early retrospective comparison of 464 patients who underwent surgery and 76 who underwent SABR for clinical stage I NSCLC at Washington University, local control at 3 years was improved with surgery for stage IA patients (96% *vs.* 89%, P=0.04) but no different for stage IB patients (P=0.89). Although no difference in disease-specific survival was seen, surgery was associated with improved overall survival, potentially also in part due to patients receiving surgery being younger, having lower comorbiditity scores, and having better pulmonary function (all P<0.001). In a matched analysis of higher risk surgery patients (n=57) to SABR patients, no difference was seen in local recurrence, disease-free survival, or overall survival at 3 years (all P>0.05) (35). In their updated T-stage matched analysis of patients treated with lobar resection (n=260) or SBRT (n=78), there was no significant difference in patterns of failure or cause-specific survival, whereas overall survival favored surgery (36).

Investigators from the Netherlands have published a series of studies comparing surgery and SABR. In a propensity score-matched analysis based on stage, age, gender, comorbidity score, lung function, and performance

 

status, locoregional control rates were higher in patients receiving SABR (n=64) than those receiving VATS (n=64) (86.9% *vs*. 82.6%, P=0.04), whereas there was no difference in distant recurrence rate or overall survival (37). In an updated propensity score-matched analysis (n=73 for each modality), survival was similar (P=0.089) at 12 months (95% *vs*. 94%) and 60 months (80% *vs*. 53%) for patients undergoing surgery and SABR, with a trend towards improved survival with surgery at longer follow-up identified (38). In a recent publication of stage I NSCLC patients treated with surgery (n=143) or SABR (n=197), survival was similar across modalities when controlling for prognostic covariables (P=0.73). When examining recurrences, local and distant control were similar but locoregional recurrences occurred more following SABR (P=0.028), suggesting a need to improve staging in SABR-treated patients (39).

Surveillance, Epidemiology, and End Results (SEER) studies and systematic reviews have also compared surgery and SABR. Among 10,923 patients aged ≥66 years with stage I NSCLC treated from 2001-2007, the majority (59%) were treated with lobectomy, whereas only 1.1% were treated with SABR. SABR was associated with a lower risk of death at 6 months (HR 0.48), whereas lobectomy had better long-term survival in fit patients (HR 0.71). On propensity-score matched analysis, SABR and lobectomy had similar survivals and both had superior survival compared with conventionally fractionated irradiation (40). Similarly, a SEER study of 9,093 patients with node-negative NSCLC treated from 2003-2009 with lobectomy (79.3%), sublobar resection (16.5%), or SABR (4.2%) reported unadjusted 90-day mortality to be highest with lobectomy and lowest with SABR (4.0% *vs*. 1.3%, P=0.008). However, at 3 years, unadjusted mortality was lowest with surgery (25.0% *vs*. 45.1%, P<0.001), resulting in SABR being associated with better overall survival at 6 months but inferior long-term overall survival. Like the elderly SEER analysis, similar survival between lobectomy and SABR was seen on propensity score-matching analysis (HR 1.01, P=0.94) (41). These findings of lower acute toxicity and better 90-day mortality but inferior long-term survival with SABR compared with surgery in an unadjusted population were further confirmed in a third SEER study (42). In a systematic review of 45 publications of stage I NSCLC from 2006-2013, there was no difference at 2 years in survival (70% *vs*. 68%) or local control for 3,201 SABR patients and 2,038 surgery patients (43).

Cost-effective analyses comparing surgery and SABR for stage I NSCLC have demonstrated conflicting results. Using Medicare-allowable charge rates, one report demonstrated SABR to be less costly than surgical intervention in high risk patients, although surgery was still found to meet the standards for cost-effectiveness due to a non-significant superiority in overall survival (44). In a separate analysis using Medicare charges, SABR was found to be more cost effective for marginally operable patients, whereas lobectomy was more cost effective for clearly operable patient (45). Using Ontario, Canada fee schedules, SABR was projected to significantly reduce overall costs and surgical gains by reducing recurrences compared with conventionally fractionated radiotherapy. In that study, SABR was found to have approximately half the upfront costs of lobectomy, but lobectomy was cost effective compared with SABR by producing more QALYs at the expense of higher cost (46). Using SEER-Medicare data, SABR was found to be less costly than surgery. However, lobectomy, but not sublobar resection, was found to be cost-effective compared to SABR (47).

Given the available literature, some have suggested SABR to be a front line therapy option in operable patients who were elderly and potentially most susceptible to surgical-related complications (48). However, given that surgery has been the gold standard for all medically operable patients (49) for the past several decades, randomized data demonstrated clear rationale to warrant SABR to be considered an optimal first-line option for medically operable patients have been lacking.

## STARS and ROSEL trials

In the June issue of *Lancet Oncology*, Chang and colleagues published their pooled analysis of two randomized trials comparing surgery to SABR for patients with operable stage I NSCLC (50). Their publication, the first randomized report comparing surgery and SABR for medically operable patients, combined data from the STARS (StereoTActic Radiotherapy *vs*. Surgery) international randomized phase III trial comparing CyberKnife® SABR with surgical resection and the ROSEL (Radiosurgery Or Surgery for operable Early stage non-small cell Lung cancer) VU Medical Centre Amsterdam and the Dutch Lung Cancer Research Group randomized phase III trial comparing SABR or surgery.

In the STARS trial, patient with tumors ≤4 cm and operable clinical stage I NSCLC either received surgical resection and mediastinal lymph node dissection or SABR to 54 Gy in three fractions (peripheral) or 50 Gy in

 

4 fractions (central). Interestingly, there was a potential bias in favor of the surgical arm in that adjuvant chemotherapy was not allowed with the SABR arm but could be given to surgery patients found to have positive margins or be upstaged to have pathological N1 or N2 disease, with adjuvant chemotherapy in this setting well established to improve overall survival (51,52). In the ROSEL trial, patients with tumors ≤3 cm with operable clinical stage IA NSCLC either received surgical resection (lobectomy was preferred but limited resection was acceptable) or SABR to 54 Gy in three fractions (peripheral) or 60 Gy in five fractions (central and tumors with broad contact to the thoracic wall). Histological confirmation of a NSCLC diagnosis was required in the STARS trial but not the ROSEL trial, although lesions had to be new or growing and radiographically consistent with NSCLC and avidity on PET/CT (50).

Although both the STARTS and ROSEL trials closed early due to poor accrual, a pooled analysis of the two trials was conducted by Chang *et al*. with a primary outcome of overall survival. Fifty-eight patients were enrolled and randomized to SABR (n=31) or surgery (n=27), with no differences in patient or tumor characteristics found between arms. Overall survival was found to be significantly higher among patients randomized to SABR (P=0.037; HR 0.14; 1-year survival 100% *vs*. 88%, 3-year survival 95% *vs*. 79%). This survival difference was significant in the STARS trial alone (P=0.0067) but not the ROSEL trial (P=0.78). The authors hypothesized that this survival difference was related to surgery resulting in worsening comorbidities after surgical reduction of lung function. This is in keeping with the Kaplan-Meier survival curves that Chang *et al*. present in image 2A, in which there is an early separation in survival in favor of SABR that is consistent with perioperative mortality from surgery, but similar survival between the two arms thereafter (50). At 3 years, there was no difference in local control (SABR 96% *vs*. surgery 100%, P=0.44), regional nodal control (90% *vs*. 96%, P=0.32), metastatic-free survival (97% *vs*. 91%, P=0.42), and recurrence-free survival (86% *vs*. 80%, P=0.54) (50).

Toxicity also generally favored the SABR arm. The lone case of treatment-related mortality occurred in the surgery cohort. In the SABR arm, no patient developed grade 4 or 5 toxicity, and 10% developed a grade 3 adverse events (6% dyspnea/cough, 10% chest wall pain, 3% fatigue, 3% rib fracture; all of these events occurred in 3 total patients). In the surgery arm, in addition to the 4% with a grade 5 toxicity, 44% developed grade 3 or 4 adverse events that included dyspnea, lung infections, chest pain, bleeding, fistula, hernia, anemia, fatigue, nausea, weight loss, and cardiac arrhythmias (50).

Given that the STARS trial only enrolled 36 of its intended 1,030 patients and the ROSEL trial only enrolled 22 of its intended 960 patients, the results reported by Chang *et al*. should be interpreted with caution, particularly the local, nodal, or distant failure rates and recurrence-free survival since follow-up was limited and so few events occurred during the study follow-up period resulting in very limited study power to detect differences between arms. Additional caution should be taken since the survival reported in the SABR arm is higher than what has generally been previously reported in SABR studies. However, this may be due to all patients receiving a SABR regimen with a biologically effective dose >100 Gy, which has previously been shown to allow for better local control and overall survival with SABR (53), and also since the current study included patients with smaller lesions, better performance statuses, fewer comorbidities, and more thorough pretreatment staging than most prior SABR reports. In contrast, only 5 of 27 patients in the surgery arm of the pooled analysis underwent a video-assisted thoracoscopic (VATs) lobectomy. It is possible that the perioperative mortality and thus overall survival for the surgery arm would have been higher had more patients underwent VATs, as has recently been demonstrated (54).

## Future directions

Given the historical perception by many physicians there is lack of equipoise between the treatment modalities and given that many patients have been unwilling to undergo randomization between the two treatments that have such a different toxicity profile, trials comparing SABR and surgery will continue to have difficulty with accrual (55). The ACOSOG Z4099/RTOG 1021 randomized phase III trial of sublobar resection with or without brachytherapy versus SABR in high risk patients with stage I NSCLC, the only other phase III randomized trial conducted to date other than the STARS and ROSEL trials, is unlikely to provide any significant additional insight in the debate of SABR versus surgery given that it closed early in 2013 due to lack of accrual and is without publication. That study also differed from the STARS and ROSEL trials in calling for sublobar instead of lobar resection for surgery patients. However, additional insight from two upcoming randomized trials may be forthcoming. The VALOR trial

 

(Veterans Affairs Lung cancer surgery Or stereotactic Radiotherapy) is scheduled to open in the United States within the year, and the SABRTooth trial (a multicentre pilot and feasibility study that will compare SABR and surgery for peripheral stage I NSCLC in patients thought to be at higher risk of surgical complications) is also planned to open in the United Kingdom.

## Conclusions

Chang and colleagues should be highly commended for a notable publication and the first phase III randomized report comparing SABR and surgery. Their findings that SABR for operative stage I NSCLC is highly effective and has a mild toxicity profile adds further credence to the notion that there is equipoise between the two treatment options and clearly supports SABR being considered a first-line option for treatment of operable stage I NSCLC.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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