

Stereotactic Body Radiation Therapy for Early - Stage, Inoperable Non-Small Cell Lung Cancer

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The first to use hypofractionated radiotherapy similar to SBRT were Karolinska Hospital in Sweden. They used it for extra cranial sites like lung, liver, and retroperitoneal tumors in the mid-1990s.¹ Its preliminary report consisting of outcomes of 31 patients treated with stereotactic radiotherapy and the radical radiotherapy using parallel opposed beams with small postage-stamp fields covering the primary tumour alone in the Netherlands were encouraging^{1,2} with the three-year loco regional control rate of 94%.² Given the promising results and significant improvements in technology, this technique was widely used over the next several years. These findings, therefore, coupled with significant advances in technology, led to the widespread use of this technique over the next several years. The landmark study done by Onishi et al.³ in Japan revealed that achieving a BED greater than 100 Gy is necessary for local control of early-stage NSCLC. Local control of lesions receiving SBRT with BED more than 100 Gy was 92% versus 74% for patients receiving SBRT with BED less than 100 Gy. This study served as the basis for prospective dose-escalation trials. Notably, the BED was greater than 100 for all the most commonly used doses and fractionation schedules for lung SBRT (50 Gy in 5 fractions, 48 Gy in 4 fractions, 54 Gy in 3 fractions). Many significant dose-escalation trials were conducted at Indiana University and guided the standard lung SBRT dose and fractionation schemes used now. The primary phase I dose-escalation trial by Timmerman et al.⁴ comprised 37 patients with T1-2N0 biopsy-proven NSCLC treated with SBRT. It found out that the maximum tolerated dose is 60 Gy in 3 fractions. There were local recurrences in 6 patients in this study, all of whom received less than 54 Gy in 3 fractions. A subsequent phase II trial affirmed an excellent 2-year local control rate of 95% but identified an increased severe toxicity rate for central tumors located within 2 cm of the proximal bronchial tree⁵. Six patients had treatment-related deaths, and 4 of those six patients had central lesions.

These initial single-institution studies paved the way for cooperative group trial by RTOG. The RTOG 0236 was a phase II multi-institution trial consisting of patients with medically inoperable, stage I to II NSCLC with peripherally located tumors less than 5 cm.⁶ A dose of 60 Gy in three fractions was prescribed to the patients. Nevertheless, when accounting for dose heterogeneity due to the difference in tissue density between the lung and soft tissue in treatment planning, the equivalent dose was 54 Gy in 3 fractions. Long-term follow-up revealed 5-year local control of 93%, lobar control of 80%, a distant failure rate of 31%, and overall survival 40%⁷, which are consistent with large retrospective series. Notably, the low overall survival in both prospective and retrospective studies for SBRT for lung

cancer in medically inoperable patients is mostly due to deaths from inter-current disease and not cancer-related deaths. These small-scale, preliminary SBRT studies led to several subsequent cooperative group trials. It includes the RTOG 0813 trial for central lesions and RTOG 0915 for single-fraction SBRT.

RTOG 0813 was a phase I/II dose-escalation study intended to define the maximum tolerated dose (MTD), effectiveness, and toxicity of stereotactic body radiotherapy (SBRT) for NSCLC, which are located centrally. In this study, medically inoperable patients with biopsy-proven, centrally located NSCLC were treated with 5-fraction SBRT ranging from 10 to 12 Gy per fraction (50–60 Gy total) delivered over 1.5 to 2 weeks.⁸ Three-year local control was excellent, approximately 85% with these 5-fraction regimens for patients receiving 11 to 12 Gy per fraction. The MTD for this study was 12.0 Gy/fx. It was associated with 7.2% dose-limiting toxicities (DLTs), which was less than the protocol-specified limit of 20%. There were 5 DLTs in the first year after treatment in patients receiving 10.5 Gy to 12 Gy per fraction. The tumor control rates were also high. The outcomes in this group, which consists of medically inoperable, mostly elderly patients with comorbidities, is comparable with that of patients with peripheral early-stage tumors. However, it is of utmost importance for the judicious selection of dose and fractionation schedules for central lesions to balance local control with the risk of severe toxicities. Despite the MLD being 12 Gy per fraction in this trial, the number of late severe toxicities prevent this dose from being uniformly accepted.

A phase I/II dose-escalation trial by Roach MC et al., from Washington University, also found that SBRT for central NSCLC using 11 Gy × 5 fractions is tolerable and has excellent local control, with the 2-year local control being 85% for 11 Gy × 5.⁹ However it was associated with severe late toxicity in some patients.¹⁰ Toxicities were: 6% grade 3 to 4 cardiac or pulmonary toxicities, and 27% grade 3, 12% grade 4, and 4% grade 5 late toxicities.

A phase I/II trial conducted by investigators at MD Anderson Cancer Center used stereotactic ablative radiation therapy (SABR; 50 Gy in 4 fractions) for centrally located non-small cell lung cancer (NSCLC). It explored the use of 70 Gy in 10 fractions for cases in which dose-volume constraints could not be achieved with the previous regimen. It also suggested modified dose-volume constraints.¹⁰ Central tumors were defined as those within 2 cm of the proximal bronchial tree, mediastinal structures (e.g., esophagus, major vessels), or a vertebral body. Ultra central lesions were those that did not meet the 4-fraction dose

constraints, often because of direct abutment with an organ at risk. Three-year local control was excellent at 96.5%, and only 2% of patients had grade 3 or higher toxicity.

Likewise, Hilal Tekatli et al. from the Netherlands have shown a high local control rate with 60 Gy in 12 fractions in patients with tumors abutting the trachea or mainstem bronchus.¹¹ But, their experience also emphasizes the possible risk of severe toxicity in this patient population. The study revealed that 38% of patients developed grade 3 toxicity and 15% grade 5 pulmonary hemorrhage. Thus, patients with ultra central tumors abutting major vessels, the esophagus, or the trachea are at risk for severe toxicity even with moderately hypofractionated (non-SBRT) regimens (10–12 fractions).

RTOG 0915 was a randomized phase II trial that compared 2 SBRT dosing schedules. It compared 34 Gy in 1 fraction versus 48 Gy in 4 consecutive daily fractions for medically inoperable stage I peripheral NSCLC.¹² One-year toxicity rates were the primary endpoint. Eighty-four patients were eligible for analysis, with 39 in the single fraction arm and 45 in the other arm. The median follow-up was 30.2 months. Rates of grade 3 or higher toxicity were noted in 3% of patients in the 34-Gy in 1 fraction arm and 11% of the 48-Gy in 4 fractions arm. Local control rates were 89% and 93%, respectively, and overall survival of 30% versus 41% in this medically inoperable patient population. Distant failure was the most common site of failure, occurring in about 40% of patients. Therefore, on the whole, prospective studies indicate that SBRT offers patients with early-stage NSCLC high rates of 5-year local control (approx 93%), with patients primarily failing in the regional lymph nodes (approx 20%) and distant metastases (30–40%).

Stereotactic body radiation therapy for early-stage, operable non-small cell lung cancer

Traditionally, surgery has been the standard of care for early-stage operable NSCLC patients.¹³ The landmark Hammersmith study in the 1950s also reiterated it, stating that patients with early-stage NSCLC had improved overall survival with pneumonectomy or lobectomy compared with conventionally fractionated radiation.

Surgical strategies have the advantage of staging the mediastinum, which is not possible with SBRT. Although PET-CT scans are reasonably sensitive and specific in identifying mediastinal adenopathy,¹⁴ an invasive mediastinal staging through mediastinoscopy or endobronchial ultrasonography-guided lymph node aspiration can be performed if there are suspicious lymph nodes on chest CT or PET-CT. In recent times, several groups have studied and evaluated the possibility of SBRT for patients with early-stage, operable NSCLC because of the good local control and the favorable toxicity profile of SBRT.

JCOG (Japan Clinical Oncology Group) 0403 was a phase II trial of SBRT for Operable T1N0M0 NSCLC. The prescription was 48 Gy at the isocenter in 4 fractions over 4–8 days. The primary endpoint was the three-year survival. Sixty-five operable patients were registered in this study

from 15 institutions, and 64 eligible patients were included in efficacy analysis 40% of whom were surgical candidates.¹⁵ The primary endpoint was 3-year overall survival. Consistent with modern lobectomy series¹⁶ 3-year overall survival was 76.5%, local control 85.4%, with 25% regional and 33% distant failures. Grade 3 toxicity rates relating to dyspnea, pneumonitis, and chest pain were low at 6%. These results confirmed the efficacy and safety of SBRT, which has the potential to be an alternative to surgery for operable T1N0M0 NSCLC.

RTOG 0618 was another new phase II trial of 26 operable biopsy-proven peripheral T1 to T2, N0, M0 non-small cell tumors no more than 5 cm in diameter.¹⁷ The setting was a multicenter North American academic and community practice cancer center consortium. The SBRT prescription dose was 54 Gy delivered in 3 18-Gy fractions over 1.5 to 2 weeks. The 4-year estimates of disease-free and overall survival were 57% and 56%, respectively. Median overall survival was 55.2 months. With a median follow-up of 4 years, local control rate was 96%, regional failure 12%, and distant metastases 12%. Four patients had grade 3 toxicity. There were no grade 4 to 5 toxicities reported.

There were two other randomized phase III trials simultaneously being conducted in the USA and Europe. They are Randomized Study to Compare CyberKnife to Surgical Resection In Stage I Non-small Cell Lung Cancer [STARS] and Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer [ROSEL] respectively. Both these trials recruited patients with early-stage operable NSCLC. The STARS trial was done at MD Anderson. It required pathological diagnosis and randomized patients to lobectomy with nodal dissection versus SBRT with 54 Gy in 3 fractions (peripheral lesions) or 50 Gy in 4 fractions (central lesions).²⁶ The ROSEL trial was conducted in the Netherlands and allowed patients without a pathologic diagnosis (PET scan only without biopsy). Patients on this trial needed to have a peripheral lesion and were randomized to surgery (as in STARS) versus SBRT with 54 Gy in 3 fractions or 60 Gy in 5 fractions. However, both trials failed to accrue and were abandoned early.

A pooled analysis of these two trials was reported by Chang JY et al.¹⁸ 58 patients were enrolled and randomly assigned (31 to SBRT and 27 to surgery). Median follow-up was 40.2 months for the SBRT group and 35.4 months for the surgery group.²⁶ The overall survival was higher in the SBRT group (95%) versus 79% in the surgery group, although recurrence-free survival was similar in the two groups (86% vs. 80%, respectively; $P = 0.54$). In the surgery group, one patient had a regional nodal recurrence, and two had distant metastases. In the SBRT group, one patient had local recurrence, four had a regional nodal recurrence, and one had distant metastases. Toxicity was also worse in the surgery group: rates of any grade 3 to 4 toxicity were 10% for SBRT patients and 44% for surgical patients. Dyspnea and chest/chest wall pain were the most common grade 3 toxicities overall. Grade 3+ lung infections, bleeding, anemia, nausea, weight loss were noted only in the surgical group.

Data from the National Cancer Database analyzing the post-treatment mortality after surgery and SBRT for Early-Stage NSCLC done by William A Stokes et al. was comparable with the pooled STARS/ROSEL analysis. It confirms the finding of increased toxicity with lobectomy.¹⁹ They identified 76,623 who underwent surgery and 8,216 who received SBRT. In the cohort, mortality rates were moderately increased with surgery versus SBRT (30 days, 2.07% v 0.73%; $P < .001$; 90 days, 3.59% v 2.93%; $P < .001$). Compared with SBRT, surgical mortality rates were higher with the increase in the extent of resection also.

Early stage inoperable NSCLC SBRT Dose - fraction schedules:

Study	Year	Dose/Fractionation
RTOG 0915	2019	34 Gy \times 1 vs 12 Gy \times 4 = 48 Gy
RTOG 0813	2019	10–12 Gy \times 5 = 50–60 Gy
Roach MC et al., Washington University	2018	
Chang (MDACC)	2014	12.5 Gy \times 4 Ultracentral: 7 Gy \times 10
RTOG 0236	2014	20 Gy \times 3 = 60 Gy
Onishi et al	2007	3–12 Gy \times 1–25 = 18– 75 Gy
Nyman et al	2006	15 Gy \times 3 = 45 Gy
Timmerman et al	2006	20–22 Gy \times 3 = 60–66 Gy
Nagata et al	2005	12 Gy \times 4 = 48 Gy
Uematsu et al	1998	30–75 Gy/5–15 fractions
Slotman et al	1996	4 Gy \times 12 = 48 Gy

Early stage operable NSCLC SBRT Dose - fraction schedules:

Study	Year	Dose/Fractionation
RTOG 0618	2018	18 Gy \times 3 = 54 Gy
STARS/ ROSEL	2015	Predominantly 18 Gy \times 3 = 54 Gy
JCOG 0403	2015	12 Gy \times 4 = 48 Gy
Lagerwaard et al	2012	7.5–20 Gy \times 3–8 = 60 Gy

Ongoing trials

Although surgery continues to be the standard of care for early-stage NSCLC, SBRT appears to provide comparable local control and survival to lobectomy^{16,18}. The data from STARS/ ROSEL are essential and interesting. However, it has not shown any superiority of SBRT over lobectomy. These studies' significant limitations include a small sample size, the inclusion of patients without pathologic diagnosis (ROSEL), higher surgical toxicity than other trials, and differing follow-up schedules. Several ongoing randomized trials (Veterans Affairs Lung Cancer Surgery Or Stereotactic Radiotherapy Trial (VALOR)²⁰, Stablemates²¹, and Radical Resection versus Ablative Stereotactic Radiotherapy in Patients With Operable Stage I NSCLC (POSTILV)²² aim to answer this critical question of whether lobectomy or SBRT has superior tumor control and/or toxicity profile for early-stage operable NSCLC. Although the results of these trials are awaited, it can safely be concluded from the large amount of prospective data that lung SBRT is a highly effective and safe means by which to treat early-stage NSCLC.

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