

Stereotactic Ablative Body Radiation for Stage I Lung Cancer in Israel: A Retrospective Single-Center Report

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ABSTRACT: **Background:** Stereotactic ablative radiation therapy (SABR) is the application of a very high radiation dose to a small treatment volume. It is the new standard of care in medically inoperable early-stage lung cancer.

Objectives: To report the outcomes of SABR in stage I lung cancer at Sheba Medical Center since its introduction in 2009.

Methods: We conducted a retrospective chart review of patients with stage I lung cancer treated during the period 2009–2015. Survival status was retrieved from the electronic medical records and confirmed with the national registry. Local failure was defined as increased FDG uptake on PET-CT scan within a 2 cm radius of the treated region. Toxicity was estimated from medical records and graded according to common toxicity criteria for adverse events (CTCAE) version 4.03. Overall survival and local control were estimated by the Kaplan-Meier method.

Results: During the study period 114 patients were treated for 122 stage I lung cancer lesions. Median follow-up time was 27 months (range 8.2–69.5 months), median age was 76 years. Eighty-two percent of the tumors were stage IA (size ≤ 3 cm). Median survival was 46 months; estimated 3 year overall survival was 59% (95%CI 47–69%) and local control was 88% (95%CI 78–94%). Toxicity included chest wall pain in 8.4% of patients, rib fracture in 0.9%, grade 1–2 pneumonitis in 12%, grade 3 in 12% and grade 5 (death) in 0.9%.

Conclusions: SABR has been successfully implemented at Sheba Medical Center for the treatment of stage I lung cancer in inoperable patients. It is associated with excellent local control, minor toxicity and an acceptable overall survival.

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KEY WORDS: stage I lung cancer, radiation therapy, stereotactic ablative radiation therapy (SABR), stereotactic body radiation therapy (SBRT)

Stereotactic ablative radiation therapy (SABR) is the application of a very high radiation dose to a small target volume. This technique was originally developed for the treatment of brain lesions in 1949 by the Swedish neurosurgeon Lars Leksell [1]. The utilization of similar techniques for thoracic tumors was delayed due to the lack of suitable imaging and the complexities of respiration-associated organ movement. The development of four-dimensional computed tomography (CT) scans combined with three-dimensional imaging attached to linear accelerators facilitated the application of stereotactic ablative radiation to the thorax [2]. Treatment is usually given in 3–8 fractions in an outpatient setting, is non-invasive and does not require sedation or anesthesia. As we reported in a recent review, SABR is an attractive option for the treatment of stage I lung cancer in the frail or medically inoperable patient in view of its excellent local tumor control (90%) and low risk of toxicity [3]. Recently, this treatment was recommended as the first-line option for medically inoperable stage I non-small cell lung cancer patients by the NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) guidelines [4,5].

Stereotactic ablative radiation therapy was established at Sheba Medical Center in 2009. In this paper we retrospectively review the outcome of stage I lung cancer patients treated with SABR between the years 2009 and 2015 in order to determine whether we could reproduce the excellent local control and acceptable survival reported in the literature.

PATIENTS AND METHODS

After receiving Institutional Review Board approval, we performed a retrospective chart review of all patients who were treated with SABR for stage I lung cancer between 2009 and 2015. Patients were referred for SABR after consultation with a multidisciplinary tumor board.

While most cases were biopsy-proven malignancy, we included in our analysis also patients without tissue diagnosis. All these cases were discussed by the multidisciplinary tumor

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board which decided that the lesion was highly suspicious for cancer based on enlarging consolidation on consecutive CT scans or fludeoxyglucose (FDG) avidity on CT/positron-emission tomography (PET). The reason for omitting biopsy was the high risk of the procedure, patient refusal, or failed previous biopsy. In cases where more than one lesion was treated, only one biopsy was needed.

SABR to the lung was performed according to the protocol based on the Vrei University Medical Centre (VUMC, Amsterdam, Holland) experience [6]: patients were immobilized using a chest board, and four-dimensional CT (4D-CT) simulation was performed using the Varian Real-time Position Management (RPM) system to provide respiration-synchronized imaging. In patients with tumor motion > 1 cm amplitude, abdominal compression was employed to reduce diaphragmatic motion. Since 2013, under the study protocol, continuous positive airway pressure (CPAP) has been explored as a way to reduce tumor motion [7]. Tumor was contoured on lung windows in each phase of the respiratory cycle to create a gross tumor volume (GTV). The GTV in all phases of the respiratory cycle were combined to form an internal target volume (ITV). The ITV was expanded by 5 mm in all directions to create a planning target volume (PTV). The dose was prescribed to the 80% or 90% isodose line to assure adequate coverage and hot spots within the tumor. The treatment technique was intensity-modulated radiation therapy (IMRT), either static or dynamic (volumetric arc modulated therapy). Calculation was performed using the pencil beam and in recent years the AAA algorithm (Eclipse, Varian, Palo Alto, CA, USA) with heterogeneity correction. The dose prescription was 54 Gy in 3 fractions for peripheral lesions not adjacent to the chest wall, 50 Gy in 5 fractions for lesions adjacent to the chest wall, or 60 Gy in 8 fractions for centrally located lesions within 2 cm of the proximal bronchial tree or mediastinal structures. Cone beam CT (CT performed on the treatment couch) was performed immediately prior to each fraction, and couch position was adjusted automatically. Treatment was delivered by the Varian Trilogy or True beam linear accelerator.

Post-treatment follow-up included chest CT scan at 3–6 month intervals during the first 2 years after treatment. For patients in whom radiation induced radiological changes (especially round consolidation) did not resolve by 12 months, PET/CT was performed in an attempt to distinguish between radiation-induced changes and tumor.

Survival status was retrieved from the electronic medical records and verified with the national registry. Tumor local control was assessed by medical charts, chest CT scan, or PET/CT up to the last available assessment. Local failure was confirmed by increased FDG uptake on PET/CT within a 2 cm radius of the treated region [8]. Toxicity data were retrospectively estimated from medical records and graded according to common toxicity criteria for adverse events (CTCAE) version 4.03.

Statistical analysis was done with STATA 13 software. Survival was analyzed using Kaplan-Meier estimates. Cox regression analysis was used to assess the effect on survival of stage, histology and dose variables including the biologically effective dose (BED) calculated according to the linear quadratic model: $BED = N \cdot d \cdot [1 + d/\alpha]$ where N is the number of fractions and d is the dose per fraction, and (α/β) is estimated to be 10 for lung cancer.

RESULTS

The cohort included 114 stage 1 lung cancer patients treated with SABR to 122 lung lesions (8 patients had synchronous primary cancers).

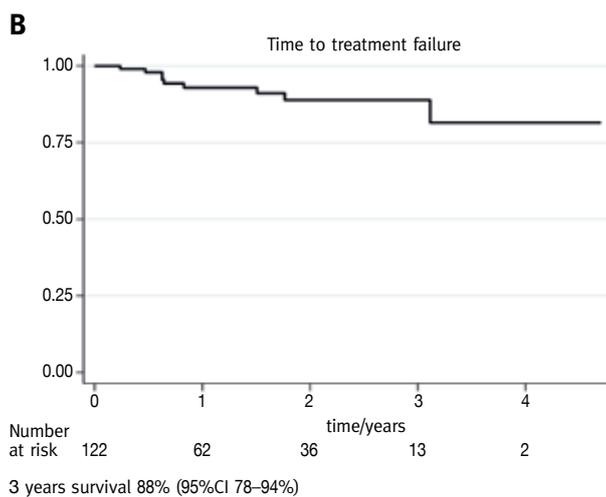
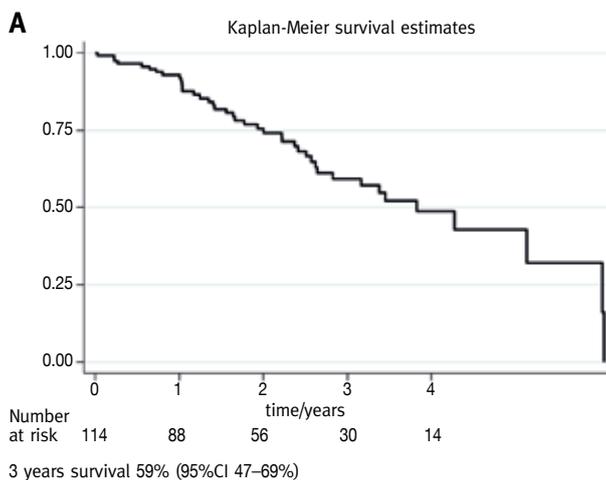
Patient's characteristics are presented in Table 1. Median age was 76 years (range 40–96). Median follow-up time was 27 months (range 8.2–69.5 months). Adenocarcinoma was the dominant histology, comprising 55 cases (45%). In 24 cases (19.7%) no biopsy was taken for tissue diagnosis. One hundred lesions (82%) were stage IA (T1: maximal tumor size ≤ 3 cm), while 22 lesions (18%) were stage IB (T2: > 3 cm and < 7 cm). The most frequent dose prescription was 50 Gy given in 5

Table 1. Patients' characteristics

| | No. | % |
|-------------------------|-----|-------|
| All patients | 114 | |
| All lesions | 122 | 100% |
| Gender | | |
| Male | 65 | 57% |
| Female | 49 | 43% |
| Age (median, range) | 76 | 40–96 |
| Stage | | |
| IA (≤ 3 cm) | 100 | 82% |
| IB (3–7 cm) | 22 | 18% |
| Total dose (Gy) | | |
| 40–45 | 6 | 5% |
| 48–52 | 84 | 69% |
| 54 | 18 | 14.5% |
| 60 | 14 | 11.5% |
| Pathology | | |
| Adenocarcinoma | 55 | 45% |
| Squamous cell | 21 | 17.2% |
| NSCLC-NOS | 4 | 3.3% |
| SCLC | 3 | 2.4% |
| No biopsy | 24 | 19.7% |
| Missing data | 14 | 11.4% |
| No. of fractions | | |
| 3 | 18 | 14.7% |
| 4 | 5 | 3.5% |
| 5 | 83 | 68% |
| 8 | 13 | 11.3% |
| 10 | 3 | 2.5% |
| BED | | |
| BED < 100 | 7 | 5.7% |
| BED ≥ 100 | 115 | 94.3% |

NSCLC-NOS = non-small cell lung carcinoma-not otherwise specified. SCLC = small cell lung carcinoma, BED = biologically effective dose

Figure 1. Kaplan-Meier estimates of **[A]** overall survival and **[B]** local control for stage I lung cancer treated with SABR at Sheba Medical Center during the years 2009–2015



fractions. The biologically effective dose (BED) was ≥ 100 Gy in 94.3% of patients.

Median survival for the entire cohort was 46 months, and estimated 3 years overall survival was 59%; 95% confidence interval (95%CI) 47–69% [Figure 1A]. For stage IA and IB, median survival was 51.3 and 41.4 months respectively; differences were not statistically significant.

Estimated 3 years local control was 88% (95%CI 78–94%) [Figure 1B]. Survival and local control were not correlated with histology or dosimetric variables. Figure 2 shows an example of SABR treatment in a patient with a squamous cell carcinoma of the left lower lobe. In this patient there was complete resolution of the tumor one year after treatment. Six patients had local failure: one patient was fit enough and underwent lobectomy and

Figure 2. Example of treatment plan and response to SABR treatment. An 86 year old woman was diagnosed with squamous cell carcinoma of the left lower lobe. **[A]** Axial view of the CT showing the tumor. **[B]** One year post-SABR, disappearance of the lesion with appearance of fuzziness where the dose was delivered. **[C]** SABR plan showing color wash (axial and coronal view), presenting $\geq 55\%$ dose. The dose is concentrated within the tumor

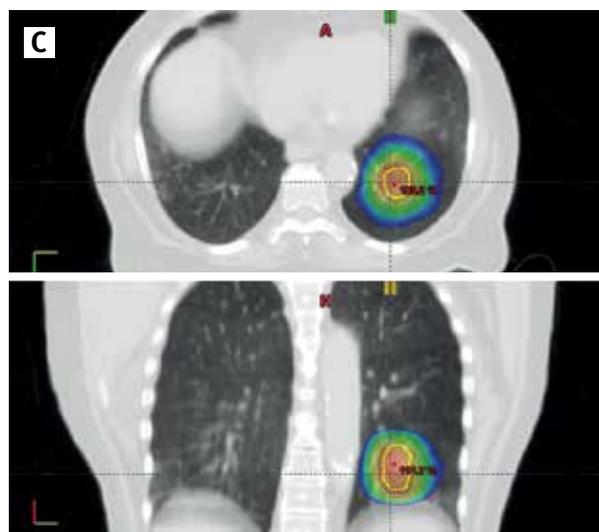
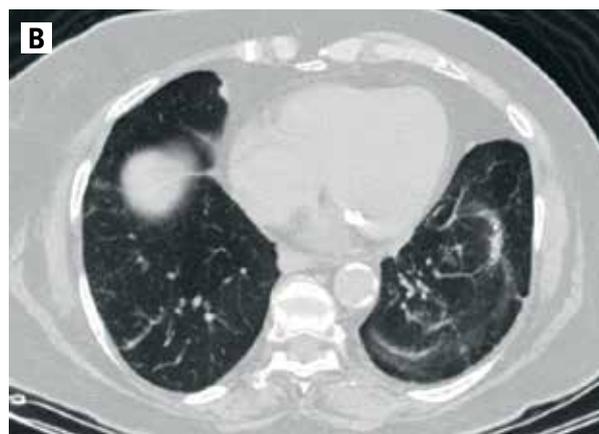


Table 2. Results of prospective and retrospective trials evaluating SABR for early lung cancer

| Author | No. of patients | Dose (Gy/No. of fractions) | Study design | 3 years overall survival | 2 or 3 years local control |
|-------------------|-----------------|----------------------------|--|--------------------------|----------------------------|
| Timmerman [9] | 55 | 60/3 | Prospective | 56% | 98% |
| Baumann [10] | 70 | 45/3 | Prospective | 60% | 92% |
| Ricardi [11] | 62 | 45/3 | Prospective | 57.10% | 87.8% |
| Guckenberger [12] | 528 | NA | Retrospective, multicenter | 47% | 79.6% |
| Guckenberger [12] | 164 | BED \geq 106 | Retrospective multicenter, subgroup analysis | 62% | 92.5% |
| Ricardi [13] | 196 | NA | Retrospective, multicenter | 68% | 89.7 |
| Solda [14] | 3201 | NA | Retrospective, multicenter | 70% | 91% |
| Current study | 114 | 50/5 54/3 60/8 | Retrospective, single center | 59% | 88% |

Gy = Gray (radiation dose unit), NA = not applicable, BED = biologically effective dose

the other five patients were found to harbor metastatic disease and were treated accordingly.

Toxicity was evaluable in 83 patients. No toxicity was seen in 56 (67.4%) of these 83 patients. Chest wall pain was recorded in 7 patients (8.4%); however, fracture was diagnosed in only one patient. Most patients had grade 1 chest wall pain, which presented as late toxicity (more than 3 months after the end of radiation) and gradually resolved. Mild pneumonitis (grade 1–2) with symptoms of sputum excretions or cough was seen in 10 patients (12%), appearing in the sub-acute period of 6 weeks to 3 months after treatment, and was treated with expectorants or codeine. Grade 3 toxicity that was possibly treatment-related was recorded in 12% of patients and presented in the first 3 months as chronic obstructive pulmonary disease (COPD) exacerbation (n=7) and pneumonia (n=3). Most cases resolved after antibiotic treatment and steroid administration. There was one case of death (grade 5 toxicity) caused by respiratory failure (0.9%) which occurred 8 months post-SABR treatment in a patient who had undergone a left lobectomy and subsequently developed metastatic lung cancer with prior major co-morbidities.

DISCUSSION

For patients unfit to undergo surgery for stage I lung cancer, SABR has been safely and effectively implemented at Sheba Medical Center. Furthermore, 3 years local control was 88% (95%CI 78–94%) and estimated 3 years overall survival 59% (95%CI 47–69%).

Our results are comparable to those reported from leading institutions worldwide. Table 2 summarizes the survival and local control results of three prospective trials and three large retrospective reports. All show similar results with 3 years over-

all survival of 47%–68% and local control of 87.7%–98% [9–14].

Surgery remains the gold standard for operable lung cancer patients, including anatomic complete excision of the tumor and lymph node sampling which provides full and accurate pathologic staging. SABR is an excellent choice for patients not fit for surgery, yet unlike surgery, pathological confirmation of margins and lymph nodes is not obtained and evaluation is based on imaging alone.

Comparing SABR to surgery is difficult due to a disparity in the patient populations. A Dutch single-arm trial evaluated SABR for stage I lung cancer patients who were eligible for surgery and demonstrated excellent results with SABR: median overall survival was 61.5 months and 3 years survival was 84.7% [15]. The two randomized trials that attempted to compare SABR to surgery (ROSEL and STARS) were closed early due to slow accrual. A pooled analysis of these two randomized trials (about 30 patients in each arm) showed an estimated overall survival at 3 years of 95% (95%CI 85–100%) in the SABR group compared with 79% (95%CI 64–97%) in the surgery group, thus underscoring the risk of surgery in patients with significant co-morbidities [16].

There are some limitations in our study: treatment was delivered without biopsy in 19.7% of cases. An additional limitation is the relatively short median follow-up of 27 months. While most treatment failures occur in this time window, later recurrences are sometimes seen.

Adequate dose (biologically effective dose of at least 100 Gy) was shown in several reports to be significant for local control and survival [12,17,18]. In our report, we did not find a correlation between BED and survival, but this could be attributed to the small number of patients treated with a BED of less than 100 Gy.

The toxicity profile of SABR in our cohort was favorable and comparable to previously reported series: two thirds of the patients did not have any symptoms at all and 20% had only minor symptoms. Even so, the more serious side effects of COPD exacerbation and pneumonia were seen in 12% and could not be separated from preexisting pulmonary morbidity. Toxicity resulted in death in one case.

Central tumors, located within 2 cm from the main bronchial tree, are associated with a higher risk of serious side effects due to exposure of central structures such as the esophagus, trachea, large bronchi and heart to higher doses of radiation. In a meta-analysis of these cases, the risk of grade 5 toxicity (death) was 2.7%, mostly caused by central airway necrosis or massive hemoptysis. This prompted the term “no fly zone” to this region. However, grade 5 toxicity in these cases was seen mainly with extreme hypo-fractionation of 60 Gy delivered in only 3 fractions. In a recently published meta-analysis, if treatment was given with a milder fractionation scheme, i.e., smaller fraction size and more fractions, the risk of dying was 1% [19]. We treated 16 central lesions

with smaller sized fractions, 60 Gy in 8–10 fractions, and did not observe increased toxicity or hemoptysis in these cases.

The incidence of lung cancer in the frail and elderly population is increasing due to the prolongation of life expectancy and the more widespread use of computerized tomography [20]. According to the Israeli National Cancer Registry, over a third of lung cancer patients in Israel are diagnosed over the age of 75 years [21]. While in the medically fit patients operative mortality is low, for elderly frail patients or those with significant co-morbidities such as COPD, surgical complications may result in considerable mortality, prolonged hospitalization and increased costs. This issue was addressed in a meta-analysis of patients with severe COPD treated for stage I lung cancer. The 30 day mortality was 0% post-SABR and 10% after surgery. Local control was high ($\geq 89\%$) with both treatments [22].

CONCLUSIONS

SABR was successfully implemented at Sheba Medical Center for the treatment of stage I lung cancer in medically inoperable patients, resulting in excellent local control, minor toxicity and acceptable overall survival. Physicians treating old and frail patients with early-stage lung cancer should be assured of the availability of state-of-the-art stereotactic ablative radiotherapy.

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