Case Series

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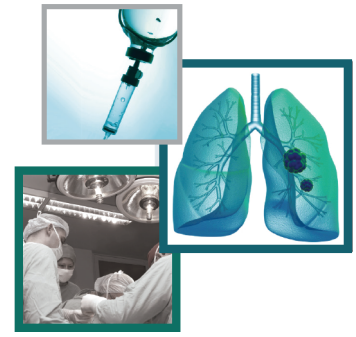
Lung Cancer Management



Lung stereotactic body radiotherapy after past ablative therapy: a single institution case series

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Practice points

- Non-small-cell lung cancer recurs 10–40% of the time after past local therapy.
- Prior to lung stereotactic body radiotherapy, vicryl mesh brachytherapy was a way to deliver highly conformal radiation after limited surgery in patients with poor pulmonary reserve.
- Patients treated with brachytherapy still suffered local failure rates of up to 10–20%.
- The results presented here showcase stereotactic body radiotherapy as a way to successfully and safely salvage patients who had prior vicryl mesh brachytherapy.
- The key point remains to utilize a hypofractionated approach and maintain adequate biological effectiveness.

Aim: Non-small-cell lung cancer recurs locally 10–40% of the time after local therapy, presenting a therapeutic challenge given poor pulmonary reserve. Herein, we seek to evaluate the safety and efficacy of stereotactic body radiotherapy (SBRT) for retreatment of such patients. **Methods:** We identified and reviewed clinical outcomes in ten patients with recurrent non-small-cell lung cancer after past vicryl mesh brachytherapy. **Results:** Ten patients with a median age of 77 were treated to a median dose of 48 Gy in five fractions. Local control at 1 year was 88%. There was one distant failure at 29 months. There was no significant toxicity after SBRT. **Conclusion:** SBRT is safe and effective when used for re-irradiation after past ablative therapies.

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Keywords: brachytherapy • lung cancer • radiofrequency ablation • SBRT • vicryl mesh

Background

Non-small-cell lung cancer (NSCLC) remains the most common cause of cancer death in the USA, accounting for 234,000 new cases per year and 154,000 deaths annually [1]. For patients with early stage NSCLC, lobectomy remains the standard-of-care treatment, assuming the patient is medically fit and can tolerate the operation. Oftentimes, due to existing co-morbidities, lobectomy is unable to be performed. It is well known that with wedge resection alone, local recurrence remains significantly higher [2]. For many years, several institutions would offer these patients wedge resection with vicryl mesh placement containing I-125 seeds to potentially decrease chance of local recurrence, typically as part of a national multi-institutional protocol [3]. Ultimately, with long-term follow-up it was discovered that there was no local control benefit to adding vicryl mesh brachytherapy, and this technique fell out of favor and is no longer a standard of care. Regardless, patients treated in that manner can experience local failure approximately 10% of the time, and present a quandary in how to appropriately and successfully offer them salvage therapy.

Ideally surgical resection would be offered but, as implied by their initial treatment strategy, would likely not be possible. Other treatment options include traditional external beam radiation, radiofrequency ablation or stereotactic body radiotherapy (SBRT) [4–7]. SBRT initially emerged as a technique to noninvasively provide ablative treatment to medically inoperable early stage NSCLC, showing excellent local control with limited toxicity

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Table 1. Patient characteristics.

Patient characteristics	Median (range)
Age	77 years (67–88)
ECOG	1 (0–2)
Gender	
Males	2 (20%)
Females	8 (80%)
Number of former smokers	10 (100%)
Number of pack years	50 pack years (10–100)
Pathology	
Adenocarcinoma	7 (70%)
Squamous cell carcinoma	1 (10%)
Large cell carcinoma	1 (10%)
NSCLC, NOS	1 (10%)
Tumor SUV of pretreatment PET scan	7.15 (2.3–12.3)
Tumor size	1.6 cm (0.6–3.1)
Treatment characteristics	
Dose Fractions	48 Gy (30–50) 5 (4–5)
BED_{10}	100 (48–105.6)
Planning target volume	24.75 cc (9.96–55.66)

BED: Biologic equivalent dose; ECOG: Eastern Cooperative Oncology Group performance status; NOS: Not otherwise specified; NSCLC: Non-small-cell lung cancer; SUV: Standard uptake value.

in appropriately selected patients [8]. Given the technique's ability to deliver a highly conformal dose of radiation with rapid fall off it was naturally used for instances of re-irradiation for recurrent lung tumors with reasonable success [9–11]. There has also been a report of using SBRT to salvage patients with local failure following vicryl mesh brachytherapy, with excellent outcomes [4]. Herein, we report outcomes in a group of patients treated with lung SBRT following past vicryl mesh brachytherapy.

Methods

We identified ten patients treated with lung SBRT in the setting of past ablative therapy including vicryl mesh brachytherapy after wedge resection in this Institutional Review Board-approved retrospective study. Patients treated with vicryl mesh brachytherapy received a prior dose of 120 Gy via I-125 after wedge resection. Six failures were at the site of the prior mesh, one in the same lobe, one in the same lung and two in the contralateral lung. All patients had past biopsy-proven diagnosis of NSCLC prior to original surgical or ablative therapy (seven adenocarcinoma, one squamous cell carcinoma and one large cell, and one NSCLC not otherwise specified [NOS]). Prior to SBRT, four patients (40%) had reconfirmation of malignancy through biopsy. The remainder of patients were treated as recurrent disease based on growth, appearance, location and uptake on PET/computed tomography (CT). All patients had appropriate pretreatment staging with CT scans of the chest, abdomen and pelvis, and FDG-18 PET-CT. Patient characteristics are outlined in Table 1.

SBRT was delivered in the outpatient setting using dose and fractionation schemes left up to the discretion of the treating radiation oncologist. All patients underwent a 4D noncontrast chest CT with 1.5–3 mm slices for treatment planning simulation to account for respiratory motion. A gross tumor volume was delineated on a free breathing scan and expanded on four expiratory and four inspiratory phases to generate an internal target volume. The planning target volume (PTV) expansion was typically 5 mm, occasionally less if directly abutting central structures at the discretion of the treating physician. Linear accelerator-based radiotherapy was delivered via 8–12 coplanar 3D conformal beams with 6 MV photons. The median dose for patients in this study was 50 Gy in 4–5 fractions, ranging from 30 to 50 Gy. The corresponding biologic equivalent dose (BED_{10}) was a range of 48–105.6 Gy with a median of 100 Gy. The median dose covering 95% of the PTV was consistent with prescribed dose. Daily megavoltage cone beam CT was used for image guidance. Figure 1 shows a representative treatment plan.

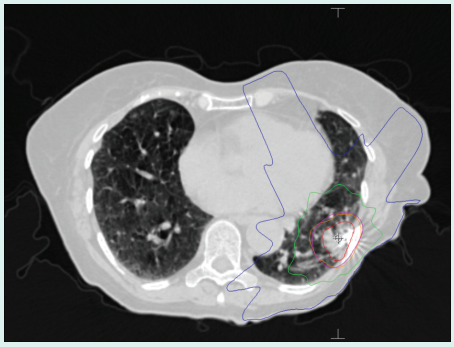

Figure 1. Axial slice from stereotactic body radiotherapy plan for patient treated to 50 Gy in five fractions to biopsy-confirmed local recurrence at site of prior vicryl mesh brachytherapy. Red contour represents internal target volume and the orange contour represents the planning target volume. The magenta, green and blue lines are the 50, 25 and 10 Gy isodose lines, respectively.

After treatment, patients were typically followed with noncontrast chest CTs or PET/CTs at least every 3 months for 1 year and every 3–6 months thereafter. Response to treatment and local/distant control was assessed via Response Evaluation Criteria in Solid Tumors (RECIST) criteria [12]. Patient characteristics and morphological features, size, location, growth and maximum SUV of the treated lesions, were reported if available and correlated with disease progression with univariate and multivariate analysis via Cox regression models [13]. Survival, local control and distant control (defined as distant metastases or contralateral lung failure) were all determined via Kaplan–Meier methodology [14]. All statistics were conducted via Medcalc.

Results

A total of two males (20%) and eight females (80%) were identified as having been treated with lung SBRT after past vicryl mesh brachytherapy. The median age was 77 (67–88) and ECOG performance status was 1 (0–2). The median time to SBRT from brachytherapy or RFA was 41 months (2–85 months). All patients had pretreatment PET/CTs with median SUV of 7.15 in the target lesion (2.3–12.3). The median nodule size was 1.6 cm (0.6–3.1 cm). The median PTV volume was 24.75 cc (9.96–55.66 cc). As above, patients were treated to a median dose of 48 Gy (30–50 Gy) in five fractions [4,5].

The median follow-up from SBRT was 46.5 months (3–97 months) and from prior brachytherapy was 93.5 months (57–133 months). All patients had follow-up imaging in the form of PET/CT or CT scans with a median number of follow-up images of six [1–12]. There were two patients who experienced local failure. One local failure was biopsy proven at 48 months and the other was highly suspicious based on appearance and doubling in size on follow-up imaging at 11 months. The resulting local control was 88% at 1 year and 66% at 4 years (Figure 2). One patient had distant failure at 29 months, resulting in a 3-year distant control rate of 86%. The median overall survival was 48 months, with 2 and 5 years survival rates of 88 and 38%, respectively (Figure 3). Given the small sample size, no predictors were identified for local control, distant control, progression-free survival or overall survival.

There was one patient who experienced treatment-related toxicity. This toxicity consisted of an increased oxygen requirement at 4 months following SBRT (requiring 2 l by nasal cannula; prior to SBRT she was not on supplemental oxygen). Given the paucity of toxicity, no comparison was able to be made between central and more peripheral tumors.

Discussion

Lung cancer remains one of the most common malignancies throughout the world and affects 234,000 patients a year in the USA. It is still the leading cause of cancer death among both men and women, resulting in 154,000 deaths annually [1]. The chance for cure remains reasonably high when found at an early stage, which is occurring more given the rise in chest CT screening for patients at a sufficiently high risk [15]. Surgery remains the standard of care for patients with early operable NSCLC. A landmark study performed by the Lung Cancer Study Group back in the late 1980s compared limited resection to lobectomy for patients with clinical Stage 1 NSCLC [2]. Results of that study showed a tripling of local recurrence with limited resection, from 6 to 18%. Given that the patient population that is affected by NSCLC, and the typical risk factors and comorbidities, these patients are

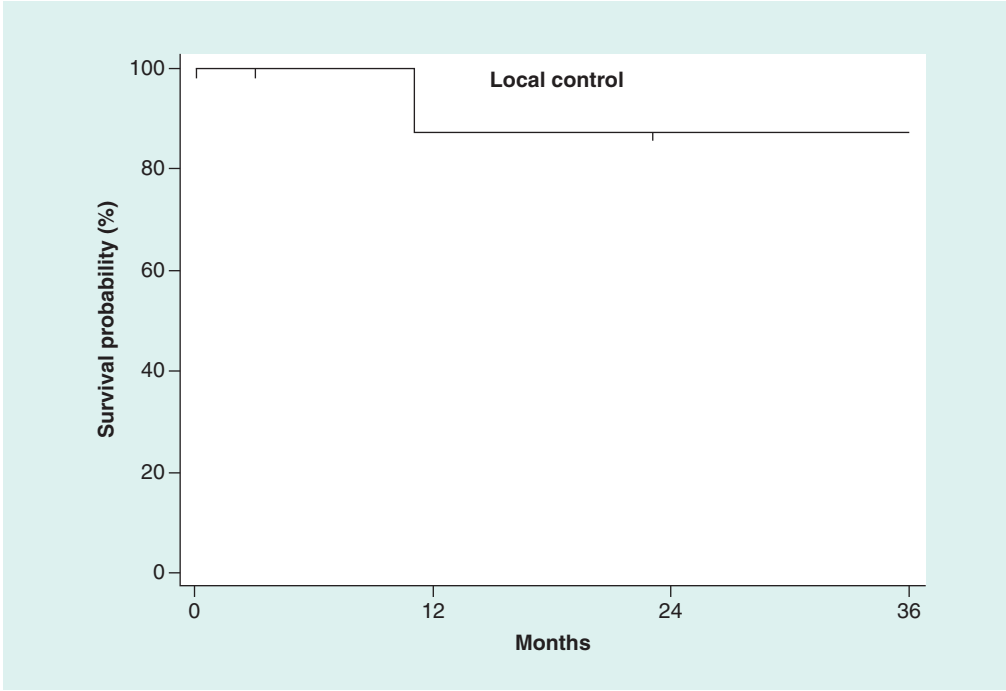

Figure 2. Local control following stereotactic body radiotherapy. Median local control was not reached. Actuarial local control at 1 year was 88%.

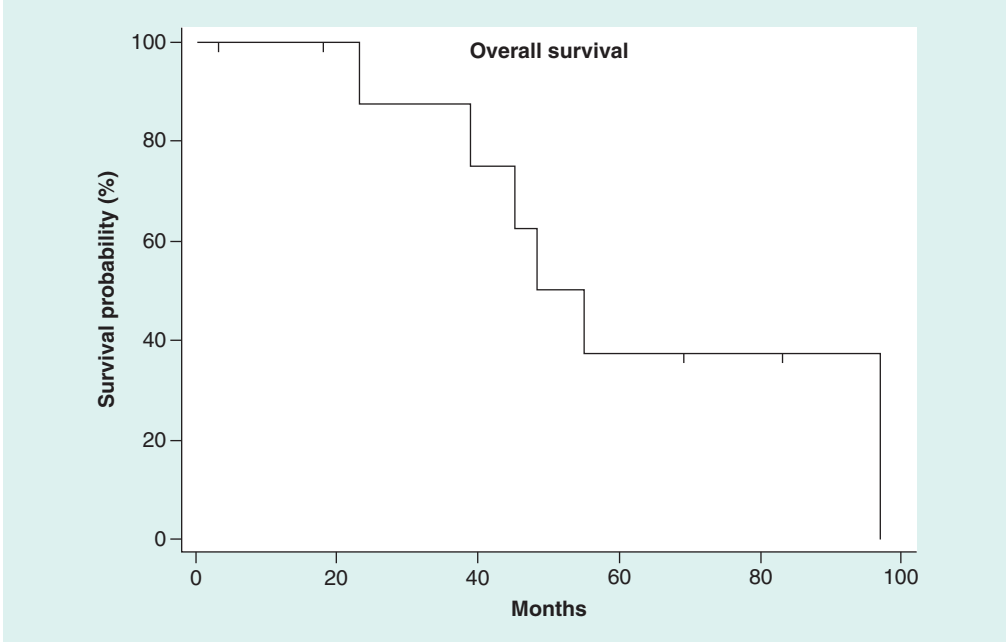

Figure 3. The median overall survival was 48 months following stereotactic body radiotherapy, with 2- and 5-year survival rates of 88 and 38%, respectively.

oftentimes unable to undergo lobectomy [16]. For such patients, there are a few reasonable alternatives that have been investigated and are discussed below.

Given the increased local recurrence seen with limited resection, the American College of Surgeons Oncology Group (ACOSOG) designed a randomized trial to compare sublobar resection with sublobar resection followed

by brachytherapy to the staple line using iodone-125 in patients who were at high risk, but operable [3]. 224 patients were randomized, with fair balance between patient characteristics in each arm. At 5 years of follow-up, local recurrence was 14 and 16.7% in the sublobar resection and sublobar resection plus brachytherapy arms, respectively (p = 0.59). There was no statistically significant difference in overall survival between the arms. Given those results, this technique and approach has gradually fallen out of favor.

For patients with poor cardiopulmonary reserve, or those preferring a less invasive approach, SBRT represents another viable option for medically inoperable early-stage NSCLC. Initial results for NSCLC showed high rates of local control in the 90% range, with minimal toxicity in appropriately selected patients (noncentral locations, size <5 cm) [7,8,17].

Given SBRT's ability to deliver a highly conformal dose of radiation with rapid fall off, its application was naturally extended to treatment of previously radiated, or even ablated, lung tumors. The group at MD Anderson published outcomes in 36 patients treated with SBRT for previously radiated lung tumors [18]. The median dose delivered was 50 Gy in four fractions. The median follow-up after SBRT was 15 months and local control at 2 years was excellent at 92%. However, the toxicity was higher compared with *de novo* lung SBRT, with half of all patients experiencing increased oxygen requirement after SBRT. Furthermore, almost a third of patients experienced chest wall pain related to SBRT. The group from the University of Kentucky has also published their results of using SBRT for re-irradiation in the lung [19]. 27 patients were retreated with SBRT to a median dose of 50 Gy with corresponding BED_{10} of 100 Gy. Median follow-up was 22 months from SBRT and local control was 89%. Nodal and distant failures were 37 and 30%, respectively. Dose selection was highlighted as doses with BED_{10} >100 Gy predicted for better progression-free survival.

SBRT has also been utilized in the setting of local failure following surgical resection [20]. A small series from the Cleveland Clinic was reported on outcomes in 40 patients (90% of which were wedge resections or lobectomy). The majority were treated with SBRT using 50 Gy in five fractions and median follow-up was 18 months. Local control was 88% in that series, and two patients developed grade 3 toxicity by way of atelectasis or soft tissue necrosis. In terms of re-irradiation after past lung brachytherapy, the data and literature are limited to a single series in which 13 patients were treated with a median dose of 48 Gy in four fractions (BED_{10} = 105.6 Gy) [4]. Follow-up was 2 years from SBRT and local control was 83.9%. Overall survival was 66% and there was only one patient with Grade 3 or higher toxicity in the form of esophagitis, highlighting the importance for caution when re-irradiating centrally located lesions. The results of our study are similar, with a 1-year local control rate of 88%. Median overall survival in our study was 4 years, and we had very few distant failures (4%) showing that these local failures can truly be local only, requiring aggressive treatment. Even with a small sample size we did show some treatment-related toxicity including increased oxygen requirement. This toxicity reminds us that despite the need to be locally aggressive with re-treatment, we must still exercise caution when treating lesions in a previously irradiated or operated upon lung.

The limitations of our study include those inherent to retrospective reviews, namely selection bias. In addition, the majority of our re-treatments were in peripherally located lesions, which can explain the relatively low rate of toxicity seen here. In addition, we did include two patients with contralateral failures to help highlight the different patterns of failure after past local therapy. However, this inclusion likely skews both the toxicity and the local control numbers that are presented here.

Conclusion

SBRT is an effective and relatively safe tool for re-irradiation after past brachytherapy in recurrent NSCLC. Appropriately aggressive dosing is warranted in select patients at low risk for distant disease, but caution must still be exercised when re-treating previously irradiated lung.

Authors' contributions

RE Wegner contributed in project conception and design, data analysis and interpretation, and drafting of manuscript. N Ahmed did data analysis and drafting of manuscript. S Hasan contributed in data analysis and drafting of manuscript. LY Schumacher did drafting of manuscript. A Colonias did drafting of manuscript and gave final approval.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The results presented in this study were acquired following institutional guidelines and had appropriate approval by the Institutional Review Board of Allegheny General Hospital.

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