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Original research article

Local failure after primary radiotherapy in lung cancer: Is there a role for SBRT?

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ABSTRACT

Aim: Our purpose is to construe the role of stereotactic body radiation therapy (SBRT) in the management of lung cancer from our early experience with SBRT for salvage treatment in patients with recurrent lung cancer after initial radiation therapy.

Background: Locoregional recurrences are a frequent challenge in patients treated with radiochemotherapy for locally advanced NSCLC. Conventional external beam radiation therapy (EBRT) is rarely given as salvage treatment because of the risk of toxicity. There is a paucity of published studies evaluating the role of SBRT in this clinical setting.

Materials and methods: Between 2008 and present, 10 patients with biopsy proven non-small cell lung cancer (NSCLC) underwent 14 radiosurgical procedures for salvage therapy after failing initial radiation treatment. Patients' age ranged from 54 to 88 years with a median of 74 years in 6 males and 4 females. Intervals from initial radiation treatment to salvage SBRT were 3–33 months with a median of 13 months. SBRT treatments were delivered using Intensity Modulated Volumetric Arc Therapy (VMAT). All patients received concomitant chemotherapy.

Results: Overall survival after salvage radiosurgery ranged from 6 to 41 months (mean 20 months, median 18 months). Four of the ten patients are alive with disease locally controlled. Of the remaining 6 patients, 4 had distant progression of disease with brain metastases and one had both brain and lung metastases. The other patient had a regional failure. Toxicities were found in three of the ten (30%) patients with grade I pneumonitis.

Conclusion: In our early experience, salvage SBRT is an effective modality of treating patients who failed after conventional irradiation, achieving excellent results in terms of local control with acceptable toxicity. Further prospective studies are needed to determine optimal fractionation schemes.

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1. Background

Disease recurrence is the dominant cause of death after initial treatment for lung cancer regardless of histology (NSCLC vs. small cell cancer), stage or initial treatment modality (surgery, RT, chemotherapy or combinations thereof).[1] Patterns of failure can be local (lung parenchyma, bronchial stump, chest wall), regional (mediastinal lymph nodes) or distant (brain, liver and bone). Locoregional recurrences are reported in up to 85% of the patients after radiochemotherapy for locally advanced NSCLC.[2,3]

The use of SBRT to treat early stage inoperable lung cancer is now accepted as standard of care as per NCCN guidelines.[4] There are relatively few studies evaluating the role of SBRT in patients with recurrent lung cancer.[5,6] Technical advances with better imaging including PET CT, with the ability to target not only large but also small tumor volumes, and with improved techniques of delivering highly focused and precise radiation may have the potential to give these patients the opportunity of long term remissions and even cures.[6] Until recently, it was generally assumed that once definitive EBRT had been given, further RT could not be used since it would likely exceed normal tissue tolerances or at most it could only be used for palliation since it was expected that patients would not survive long enough to experience potential late effects.[1] A few previous reports have suggested that palliative and definitive re-irradiation following fractionated radiotherapy for lung cancer is feasible.[7,8] However, the possibility of severe adverse events from re-irradiation with SBRT of the same site is still not well known. Larger clinical target volumes and central tumor location have been associated with more severe toxicity.[9,10]

2. Materials and methods

We used an Institutional Review Board (IRB) approved lung SBRT registry to identify all patients who received SBRT for local failure after primary radiotherapy of lung cancer. Between October 2008 and July 2014, 10 patients were treated with salvage thoracic SBRT for recurrent NSCLC after failed conventional radiation (8 patients) or radiosurgery (2 patients). There were 6 males and 4 females, ranging from 54 to 88 years of age with a mean of 71 years and a median of 74 years. Intervals from initial radiation treatment to salvage SBRT ranged from 3 to 33 months with a mean of 13 months. Follow-up after SBRT salvage ranged from 6 to 41 months (mean 20 months, median 18 months). Recurrence was determined clinically by FDG-PET CT or by pathologic diagnosis. RECIST 1.1 was used to evaluate response. Patients were considered to be medically inoperable by a multidisciplinary team. Guidelines for inoperability included abnormal FEV1 of <30%, severely decreased diffusion capacity of <40%, and predicted severe cardiac disease among other significant comorbidities. All patients had a Karnofsky performance status >70%. All patients received concomitant chemotherapy.

All patients were simulated using CT with IV contrast. Patients were immobilized using a "frameless" semi-rigid evacuated bag system or a body Aquaplast™. Abdominal compression was used to decrease the tumor movement due to respiration. The internal tumor volume (ITV) was identified using CT images obtained from three respiratory phases: normal, inspiration and expiration. The clinical target volume was identical to the ITV. The planning target volume (PTV) was created by expanding the ITV 3 mm in all directions to account for patient movement and setup uncertainty. Normal tissue dose constraints were used as recommended by the American Association of Physicists in Medicine (AAPM) Task Group TG 101.[11]

Treatments were delivered using a commercially available linear accelerator with Volumetric Modulated Arc Therapy (VMAT) with either single or multiple arcs of 6 MV photon beams. Daily cone beam CT (CBCT) was obtained for treatment alignment.

Dose prescription ranged from 6 Gy/fx to 20 Gy/fx delivered in three to five fractions, depending on the location of the tumor: central versus peripheral, previous radiation dose received and size of the lesion. The peripheral lung lesions far from any other structure were treated using SBRT with 60 Gy in 3 fractions of 20 Gy each, every other day. Those peripheral lesions close to the ribs were treated with 30–45 Gy in 3 fractions. Centrally located lesions received from 18 to 40 Gy in fractions of 6–10 Gy (Figs. 1 and 2). The biological effective dose (BED, with $\alpha/\beta = 10$ Gy) ranged from 28.8 Gy to 180 Gy and the total equivalent dose in 2 Gy/fx (EQD2) was 24–150 Gy.

There were 10 patients with 14 tumors treated: 9 central and 5 peripheral in location.

Tumor volumes ranged from 2.9 cc to 101.1 cc (median 34.5 cc). Integrated boost was used in three patients to deliver higher dose in the center of the lesions due to the large tumor volume and/or critical location of the tumor.

We followed the patients after salvage SBRT with CT of the chest at one month and whole body PET-CT at 3 months and then at 6-months intervals, unless there was an earlier indication of recurrence from clinical exam or other imaging studies.

All patients received concomitant platinum-based chemotherapy as directed by the medical oncology team using standard protocols. Our rationale to use SBRT for salvage was originally intended as a palliative measure. Eight patients had an in-field recurrence (IFR). Six patients had regional failure (RF). Five patients had both IRF and RF. Toxicity was assessed using the Common Terminology for Adverse Events v3.0 (CTCAEv3).[12]

3. Results

Overall follow-up/survival after salvage radiosurgery ranged from 6 to 41 months (mean 20 months, median 18 months). Four of the ten patients are alive with disease locally controlled. Of the remaining 6 patients, 4 had distant progression of disease with brain metastases and one had both brain and lung metastases. The other patient had a regional failure. None developed local failure. Using RECIST 1.1 to evaluate response in the CT scans, there were 6 complete responses, 4 partial responses and in the remaining 4 there was stable disease after treatment. Toxicity was found in three of 10 (30%) patients with grade I pneumonitis, one of them during the

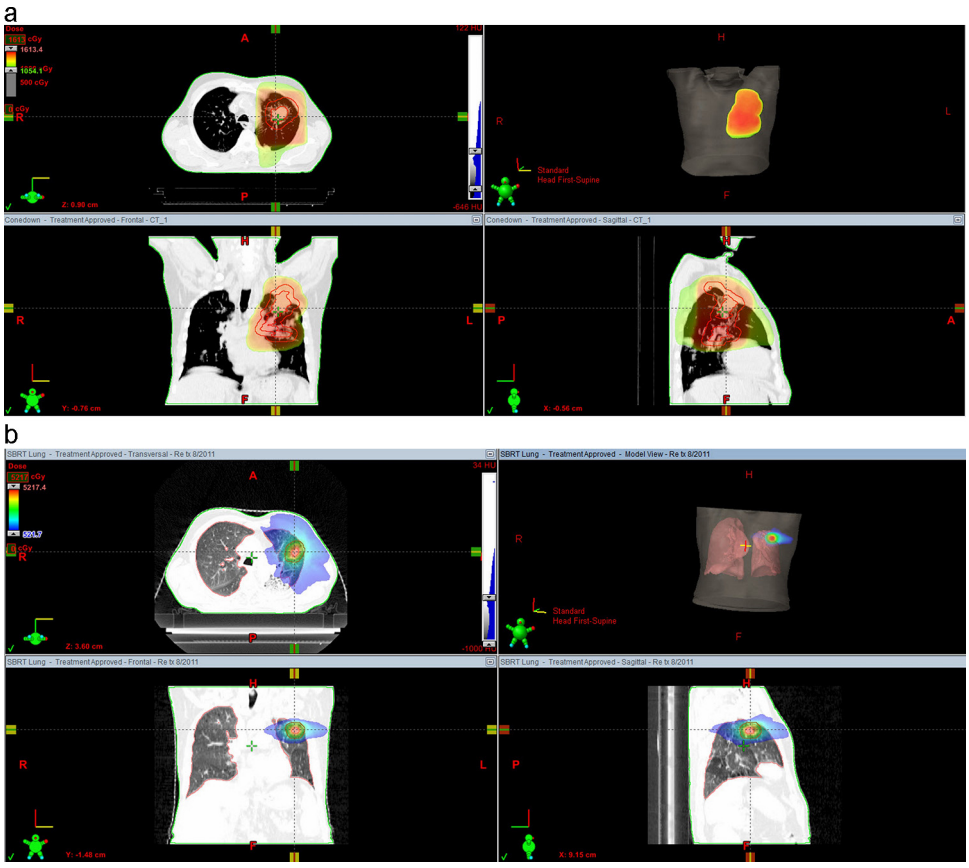

Fig. 1 – (A) Representative planning images of 74-year-old male with stage III lung cancer for initial course of conventional fractionated RT in October 2008. (B) SBRT plan for salvage of in-field recurrence in the same patient in September 2011. Dose delivered was 3 fractions of 10 Gy each to the ITV. At 41 months follow-up after SBRT retreatment the patient is alive with no evidence of disease.

treatment and two more than six months after salvage SBRT. There was no evidence of any significant esophageal toxicity. Of the four patients who are still alive, one has 41 months survival after salvage treatment and more than 6 years after the first radiation treatment course for his stage III lung cancer. Patient characteristics are shown in Table 1, including previous conventional radiation doses, toxicity and survival.

One patient treated elsewhere for a large mediastinal mass causing superior vena cava syndrome who failed systemic chemotherapy initially received conventional radiotherapy for progression of disease. We first re-treated the patient with IMRT to the mediastinum for the voluminous tumor to maximum tolerance in that particular area (Fig. 3A). A 3-month follow-up PET CT demonstrated 2 central areas of active disease prompting retreatment with SBRT to the 2 areas in question (Fig. 3B and C). The patient eventually died 8 months later from distant failure with local control in the thorax.

4. Discussion

Multiple studies have demonstrated excellent tumor control and limited toxicity with the use of SBRT. For patients with T1 and T2 tumors with a high operative risk, SBRT results in tumor control and overall survival comparable to reported results from surgery, with local control rates greater than 90%.[13] Despite the effectiveness of EBRT and the success of SBRT as a primary treatment modality for early-stage NSCLC, there is a subset of patients who develop intrathoracic recurrences after radiation treatment without evidence of distant metastatic disease. Our rationale to use SBRT for salvage for recurrent lung cancer was originally intended as a palliative measure. However, over the years we have seen results more encouraging than merely palliation. An effective salvage therapy for this group of patients is typically limited. The use of radiation in general has not been the common approach in patients with recurrent lung cancer. However, hypofractionated techniques combined with systemic treatment have been shown to be beneficial for those patients. Cetingoz et al. in 2008 reported the results of re-irradiation in 38 patients treated with various regimens of hypofractionated XRT and found symptomatic improvement and survival prolongation.[14] They emphasized the need of protecting normal structures to avoid toxicity. In univariate analysis only the interval between two courses was statically significant. Age, location of the recurrence or size of the tumor were not significant in terms of overall survival.

Trovo et al. examined their experience using SBRT in a recent retrospective study assessing toxicity and outcomes of re-irradiation in patients previously treated with radical

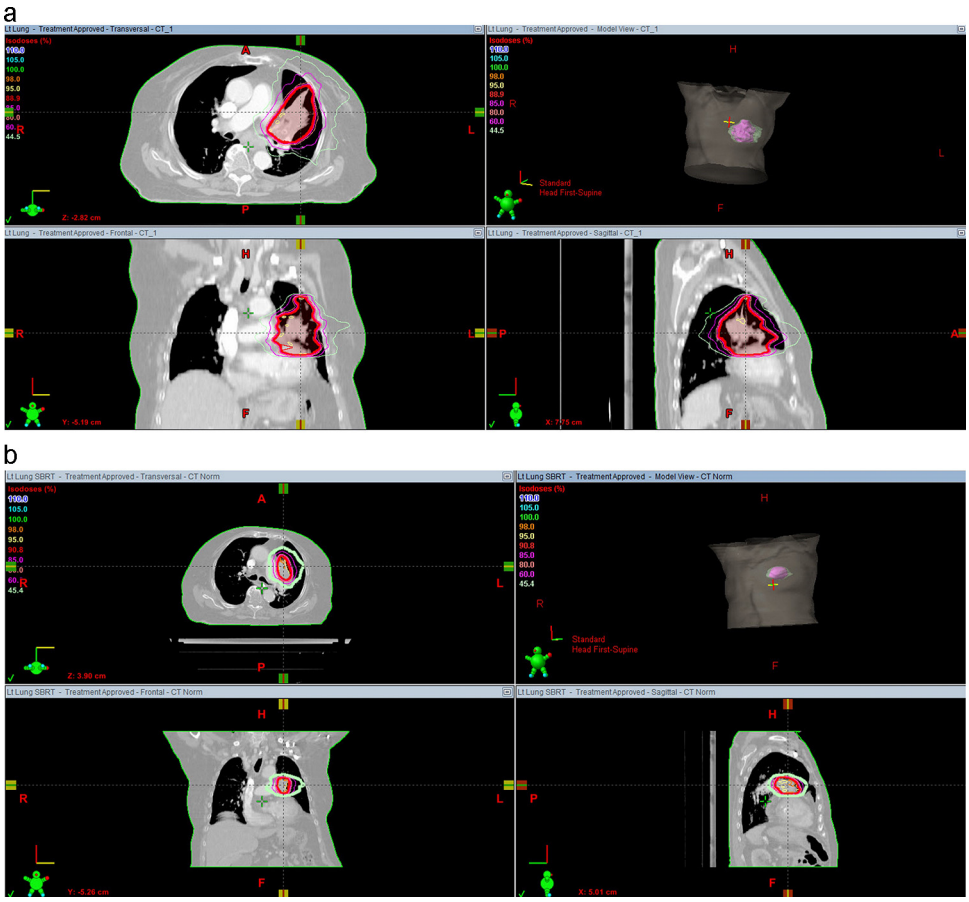

Fig. 2 – (A) Initial fractionated RT to the lung primary lung cancer (July 2012) in an 88-year-old female with stage IV lung cancer who originally presented with spine metastases in June 2012. (B) Infield relapse treated in February 2012 with SBRT: 40 Gy in 4 fractions of 10 Gy each. The patient died from multiple brain metastases with local control in August 2014.

radiation therapy (50–60 Gy). They demonstrated in a small number of patients treated with 30 Gy in 5–6 fractions that excellent local control could be obtained.[15] They did, however, report a high rate of toxicity and recommended to initiate a prospective study to determine the impact of this novel approach. Another recent paper from Karolinska Institute reported an increased incidence of Grades 3–5 toxicity in their retrospective review of 29 patients reirradiated with SBRT on 32 lung lesions (11 central, 21 peripheral).[10] They concluded that re-irradiation with SBRT is feasible with a warning of an increased risk of toxicity when irradiating centrally located lung tumors. This is consistent with the previous warning by

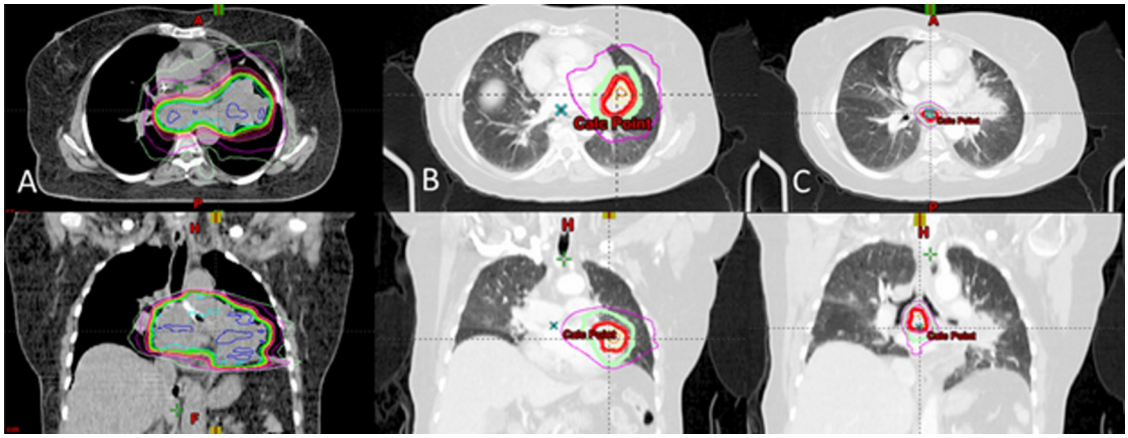

Fig. 3 – This is a 59-year-old female originally treated elsewhere for superior vena cava syndrome using conventional RT. (A) Retreatment of the voluminous tumor in the mediastinum using EBRT with 45 Gy. (B and C) Salvage radiosurgery for hilar (B) and mediastinal (C) disease after 3 months using 3 fractions of 5 Gy each with 7 Gy in the center respectively.

Table 1 – Characteristics of the whole patient cohort including dose and toxicity s/p EBRT and SBRT.

Age/sex	Dose conventional (Gy)	Failure lapse (months)	IFR	RF	Location	Dose salvage SBRT Gy/fxs	RECIST 1.1	Toxicity CTCAE 4.0	Alive	Fup/survival since last SBRT (months)	Survival since conventional (months)
75/M	56	9		Y	C (mediastinum)	8 × 3	PR	N	No	38	47
		12		Y	P (apical)	10 × 3	CR				
74/M	64.8	33		Y	P (apical)	10 × 3	CR	Late G1 pneumonitis	Yes	41	74
		35	Y		P (close to rib)	15 × 3	CR				
74/F	60	17	Y		C (mediastinum)	6 × 3	PR	N	No	37	54
73/M	63	15	Y		C	10 × 4	SD	N	No	21	36
88/F	60	19	Y		C	10 × 4	PR	N	No	6	25
54/F	66	8		Y	P	20 × 3	CR	Late G1 pneumonitis	Yes	18	26
		11		Y	C	8 × 4	CR				
71/M	45[a]	22		Y	C (mediastinum)	8 × 5	PR	N	Yes	18	40
69/F	45[b]	3	Y		C	7 × 3	SD	Acute G1 pneumonitis	No	6	9
		3	Y		C (mediastinum)	7 × 3	SD				
76/M	55.8	12	Y		P	7.5 × 5	SD	N	No	8	20
59/M	59.4	13	Y		C (Hilum (LN))	7 × 4	CR	N	Yes	8	21

Abbreviations: IFR: in field recurrence; RF: regional failure; PR: partial response; CR: complete response; SD: stable disease; RECIST 1.1: Response Evaluation Criteria in Solid Tumors (version 1.1); G1: grade 1 toxicity; N: no toxicities encountered; location C: central lesion; location P: peripheral lesion.

[a] Hypofractionated technique.

[b] Previous RT elsewhere.

Timmerman et al. regarding treatment of central tumors with SBRT in a phase II study for medically inoperable early stage lung cancer.[16] Upon close examination, it was noted that their dose was prescribed to about 67% isodose line at the periphery of the PTV resulting in a maximal tumor dose of up to 150% of the prescribed dose. One might speculate if this could be the reason for the high toxicity. In our approach, isodose line was typically around 90% and in our limited experience of 10 cases, we did not encounter such toxicity. Although we have asserted equal effort in minimizing damage to the surrounding normal tissues, dose to the surrounding lung tissue might need to be considered from a different perspective, as most of these lung tissues had already been dysfunctional due to initial irradiation.

Reyngold et al. reported a retrospective study of 39 patients with prior intra-thoracic conventionally fractionated radiation therapy for a primary, recurrent or metastatic lung tumor treated with salvage SBRT.[9] Consistent with other recently published single institution series, they showed high rates of local control achieved by using SBRT.[17–21] Their local control rate of 64% at 2 years was lower than the one from Kelly et al. with a 2-year in-field local control of 92%.[17] Reyngold et al. speculate that this could be related to the selection of fractionation schemes with lower BED for patients with direct overlap between the high-dose regions of SBRT and the prior conventionally fractionated fields.[9] Their local progression-free rate at 1 and 2 years of 77% and 64%, respectively, compare favorably with historical results of conventionally fractionated re-irradiation: 51% and 42%, respectively, reported by Wu et al.[8]; or 1-year results of SBRT experience reported by Trakul et al. of 65.5%.[18] Another study by Celada et al. of 13 patients treated with SBRT, two of them previously irradiated, concluded that SBRT seems to be a safe and effective option for medically inoperable lung cancer patients.[19]

Factors that would predict a favorable outcome in the setting of re-irradiation are largely unknown. Most data available in the recently published literature comes from small single institution studies. Overall survival, although improved, is limited by systemic progression which probably depends particularly on patient selection.[22] Distant failures are common which suggest a role for concurrent or sequential chemotherapy as suggested by Kilburn et al.[23] Our experience in the present series is too limited to make any specific recommendation in this aspect. Prospective studies are essential for standardization of the promising concept of using SBRT in the re-irradiation of recurrent lung cancer.

In our series, survival after initial radiation therapy for advanced lung cancer ranged from 9 to 74 months with a median of 31 and an average of 35 months. A closed image-based follow-up and the use of SBRT for salvage treatment may explain these encouraging results.

Based on this initial experience, we would propose the use of a regimen of salvage radiosurgery based on the location of the lesion: central versus peripheral, tolerance of adjacent critical structures, volume of the tumor and previous radiation dose. Consideration should be given to the use of an integrated boost to deliver a higher dose to the center of the tumor avoiding toxicity to surrounding normal tissue. This needs further evaluation as a feasibility or randomized study.

5. Conclusion

SBRT offers a new opportunity and hope for patients with recurrent lung cancer after failing definitive radiation therapy. This is due to its ability to deliver highly focused radiation with minimized exposure to the surrounding normal tissues. A brief review of the results of recently published clinical series attest to the virtues of SBRT in improving local control and prolonging survival in patients that otherwise will rapidly succumb to the disease. In our small series, patients tolerated the treatment well despite concomitant chemotherapy and the rate of remissions achieved with relatively minor toxicity was encouraging. Consistent with the clinical outcomes reported in the recent literature, our experience leads us to construe that the role of SBRT for recurrent non-small cell lung cancer after failing primary radiation treatment is helpful, especially in achieving improved local disease control. Further investigation will be necessary to determine optimal dose fractionation schemas and recommendations to decrease toxicity.

Conflict of interest

None declared.

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None declared.

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