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Stereotactic body radiotherapy for central lung tumors: Finding the balance between safety and efficacy in the "no fly" zone

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Abstract

Background: Stereotactic body radiotherapy (SBRT) has emerged as a highly effective technique to treat medically inoperable non-small cell lung cancer (NSCLC). Doses must be chosen carefully when treating central lesions because of the potential for significant toxicity. This study reviews the outcomes of a cohort of patients with central lung tumors treated with SBRT.

Methods: We identified 18 patients (12 women, 6 men) with central lesions that were treated with SBRT at our institution. Overall survival and local, regional, and distant control rates were assessed by Kaplan–Meier methodology. Correlations with outcomes were determined by multivariate analysis via Cox regression models.

Results: Eighty-nine percent of patients had a pathological diagnosis of NSCLC. The median dose to the planning target volume was 40 Gy (range: 30–50) in five fractions, yielding a median biologic equivalent dose (BED_{10}) of 72 (range: 48–100). The median planning target volume was 34 cc (range: 13.3–89). Local control was 87% at one year. Median overall survival was 45 months, with a two-year rate of 61%. The two-year regional control rate was 87%. $BED_{10} > 72$ predicted improved progression-free survival, with one-year rates of 100% versus 40% with increased BED ($P = 0.012$). No grade 3 or higher acute or late toxicity was observed.

Conclusions: Lung SBRT to central lesions is safe and effective when using five fraction regimens. $BED_{10} < 72$ predicted disease progression, highlighting the importance of choosing an effective dose fractionation scheme, which must in turn be balanced with potential toxicity.

Introduction

There are over 225 000 new cases of non-small cell lung cancer (NSCLC) each year in the United States, 30% of which are stage I–II.[1] For such early stage lung cancers, surgical resection remains the primary definitive approach, assuming that there are no contraindications. For patients unable to undergo surgical resection, radiation therapy, specifically stereotactic body radiotherapy (SBRT), is the primary alternative and yields excellent local control.[2,3] One of the original phase II Radiation Therapy Oncology Group (RTOG) trials examining SBRT outcomes revealed a high rate of severe toxicity (8.5% grade 5) for tumors centrally located when treated to 60 Gy in three fractions.[4] As such, caution has been advised and dosing is typically reduced or fractionation increased when approaching centrally located lesions with SBRT. The RTOG defines a central lesion as one that resides in a volume 2 cm in all directions around the proximal bronchial tree, often referred to as the "no fly zone." To date, there are a few scattered series in the literature examining the safety and efficacy of SBRT for these central lesions.[5–8] In the meantime, the results of RTOG 0813, a seamless phase I/II trial investigating SBRT for medically inoperable centrally located NSCLC, are eagerly awaited. In the present study, we review and present outcomes of a small cohort of patients with centrally located lung tumors treated with SBRT to add to the current body of literature and determine the best course of action in terms of treatment, dosing, and fractionation.

Methods

We identified 18 patients treated with lung SBRT for central lesions as defined by the RTOG between 2009 and 2017. The full RTOG definition of a central tumor is one within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi). Tumors immediately adjacent to mediastinal or pericardial pleura (planning target volume [PTV] touching the pleura) are also considered central tumors. Fifteen patients had confirmed NSCLC (7 adenocarcinoma, 7 squamous cell carcinoma, and 1 large cell), one patient was treated empirically because of comorbidities precluding biopsy, and two patients had presumed oligometastases from breast cancer and sarcoma. All patients had undergone appropriate pretreatment staging with computed tomography (CT) scans of the chest, abdomen, and pelvis and often ^{F18}fluorodeoxyglucose positron emission tomography (FDG-PET; 12 out of 18 patients).

Stereotactic body radiotherapy was delivered in an outpatient setting using dose and fractionation schemes at the discretion of the treating radiation oncologist. All patients underwent a four-dimensional non-contrast 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 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 three-dimensional conformal beams with 6 MV photons. The median dose for patients in this study was 40 Gy in five fractions, ranging from 30 to 50 Gy. All patients were treated in five fractions. The corresponding biologic equivalent dose (BED_{10}) was a range of 40–100 Gy with a median of 72 Gy. The median dose covering 95% of the PTV was consistent with the prescribed dose. Daily megavoltage cone beam CT was used for image guidance.

After treatment, patients were typically followed-up with non-contrast chest CTs or PET/CTs at least every three months for one year and every 3–6 months thereafter. Response to treatment and local/distant control was assessed via Response Evaluation Criteria in Solid Tumors.[9] Time to complete and partial response was noted. Patient characteristics, morphological features, size, location, growth, and maximum standardized uptake value (SUV) of the treated lesions were reported if available and correlated with disease progression with univariate and multivariate analysis via Cox regression models.[10] Survival, local control, regional control (defined as no new disease in mediastinum or ipsilateral lung), distant control (defined as distant metastases or contralateral lung failure), and freedom from progression were all determined via Kaplan–Meier methodology.[11] All statistics were calculated using SPSS version 20 (IBM Corp., Armonk, NY, USA).

Results

A total of 12 women and six men were included in this study. The median age was 76 years (range: 42–86) with a median Eastern Cooperative Oncology Group (ECOG) performance status of 1 (range: 0–2). Eleven nodules (62%) were on the left and seven (38%) were on the right. Ten lesions were in the lower lobe (56%), seven (39%) in the upper lobe, and one (5%) in the middle lobe. Twelve of the patients had a pretreatment PET/CT scan, with a median SUV of 6.55 (range: 2.5–15.74) in the treated lesion. On CT imaging, median pretreatment size was 2.5 cm (range: 1.4–4.5). The median PTV volume was 34.05 cc (range: 13.3–89). All patients had a smoking history with a median of 50 pack-years (range: 15–100). Median follow-up was 19.5 months (range: 3–81) from SBRT. All patients underwent clinical and radiographic follow-up.

Local control at one and two years was 87%, and the median value was not reached (Fig 1). Median overall survival (OS) was 45 months, with one and two year OS rates of 76% and 61%, respectively (Fig 2). Regional control (defined as failure in the ipsilateral lung or mediastinum) mirrored local control, with a one-year rate of 87% and the median was not reached. Median distant control (defined as distant metastatic disease or a new nodule in the contralateral lung) was 24 months, with one and two year rates of 73% and 46%, respectively. Progression-free survival (PFS) at one and two years was 67% and 42%, respectively, with a median of 24 months. There was an improvement in PFS for SBRT doses with a $BED_{10} > 72$ Gy. Median PFS

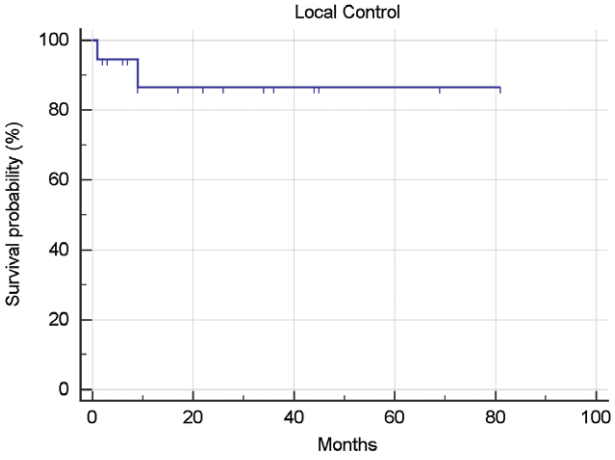

Figure 1 Local control following stereotactic body radiotherapy for centrally located lung tumors was 87% at one year.

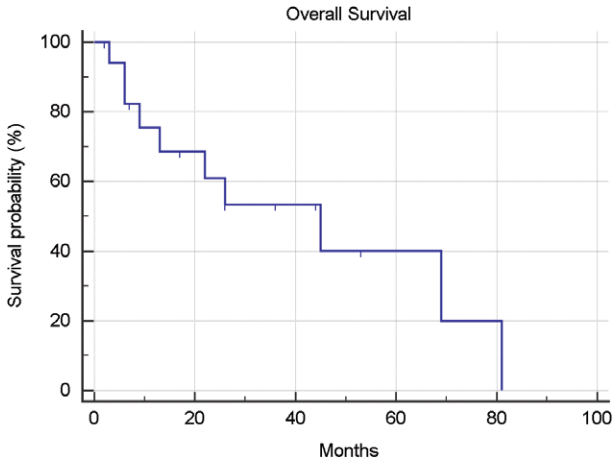

Figure 2 Median overall survival following stereotactic body radiotherapy was 45 months, with one and two year survival rates of 76% and 61%, respectively.

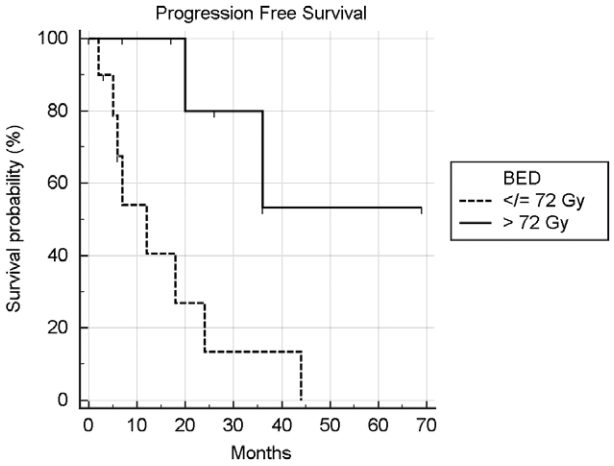

Figure 3 Progression-free survival (PFS) by biologic equivalent dose (BED_{10}) using a cutoff of 72 Gy. Median PFS was 24 compared to 12 months in favor of $BED_{10} > 72$. At one year, PFS was 100% compared to 40% ($P = 0.012$).

was 24 compared to 12 months with higher doses, and PFS at one year was 100% compared to 40% ($P = 0.012$), respectively (Fig 3). BED_{10} did not predict increased local failure. There was also a trend toward improved PFS for PTVs < 28 cc, with corresponding one year PFS of 100% versus 50% ($P = 0.092$). SBRT was very well tolerated in the patients included in this study, with no recorded grade 3 or higher acute or late toxicity.

Discussion

Non-small cell lung cancer remains a common malignancy, resulting in the most cancer-related deaths each year in the United States.[1] When presenting at an early stage, which occurs approximately 30% of the time, surgical resection is the current standard of care. Often, however, patients are deemed medically inoperable as a result of existing co-morbidities such as chronic obstructive pulmonary disease and long standing tobacco abuse. Over the past 10–15 years, SBRT has emerged as a viable alternative to surgery with results confirming its safety and efficacy.[2,3] Some toxicity has been reported with peripheral nodules, typically chest wall pain syndrome, which is usually self-limited, or rib fractures.[12] When treating central lesions, however, more serious toxicity has been noted, including an 8% risk of death when doses such as 60 Gy in three fractions were utilized.[4] In response, more protracted courses of radiation are often used (10–15 fractions) for such lesions, and have been shown to be safe.[5,13] SBRT has also been utilized for these centrally located targets, typically using 4–5 fractions (in lieu of 3) and doses < 60 Gy, resulting in excellent local control and minimal toxicity.[5–8]

RTOG 0813 is a seamless phase I/II trial that is examining dose escalation for central lesions, starting at 50 Gy in five fractions and increasing to 60 Gy in five fractions. At last report, the median follow-up was 33 months.[14] Three grade 5 toxicities (2 in the 57.5 Gy arm, and 1 in the 60 Gy arm), as well as an esophageal perforation (grade 4) have been reported. Two year local control is reported at 88–89%. Final results are pending, and will certainly be critical to determine the appropriate dosing and fractionation scheme for this group of patients.

As the results of RTOG 0813 are pending, there is some literature to help guide physicians when approaching centrally located lung lesions using SBRT or similar hypofractionated approaches. One series from the Netherlands reviewed outcomes in 63 patients with centrally located lesions. Patients were treated in eight fractions to 63 Gy ($BED_{10} = 105$).[7] The median follow-up in this series was 35 months. Local control was excellent, at 93% at three years, with three year OS of 64%. There was no grade 4 or 5 toxicity, and four grade 3 toxicities including chest wall pain, rib fracture, and dyspnea. Overall, results from this study confirm that high rates of local control can be maintained in a safe fashion using a slightly more protracted course for central lesions.

Chang *et al.* presented outcome data from 100 patients treated for central lung lesions.[5] They approached all patients up front with a plan for 50 Gy in four fractions ($BED_{10} = 112.5$ Gy), but if they were unable to meet specific dose constraints, the prescription was altered to 70 Gy in 10 fractions ($BED_{10} = 119$ Gy). Median follow-up was 30 months, and there was no grade 4–5 toxicity. There was a 1% rate of grade 3 pneumonitis, and results of this study helped to define a dosimetry goal of lung V20 < 12% to reduce the risk of lung toxicity. Three year local control was excellent at 97% with corresponding regional and distant control rates of 88% and 77%, respectively.

Chaudhuri *et al.* presented their results after treating 34 patients with central tumors at Stanford using lung SBRT to a dose of 50 Gy in 4–5 fractions (BED_{10} = 100–112.5 Gy).[6] Median follow-up was 18 months, two year local control was 90%, and median OS was 38 months. They reported a single episode of grade 4 pneumonitis and two cases of grade 3 chest wall toxicity. Horne *et al.* treated 40 patients with central tumors at a dose of 48 Gy in four fractions (BED_{10} = 105.6 Gy).[8] The median follow-up was 16.5 months and local control at two years was excellent at 88%. Median OS was 23 months and there were four cases of grade 3 toxicity, 50% of which were hemoptysis related to airway dose.

The results of the current study mirror those discussed, with a local control rate at two years of 87%. As expected and has been observed in a more frail, medically inoperable patient population, OS hovers at approximately 60% at two years. Compared to the studies discussed, more of our patients had a lower BED_{10}, which on statistical analysis was found to correlate with poorer PFS (favoring doses with $BED_{10} > 72$). This difference highlights the importance of dose selection to overall control and outcome, as evidenced in the literature, which shows improved outcomes for lung SBRT with $BED_{10} > 100$.[15] Of course, the aggressiveness of the dose must be balanced with the risk of serious toxicity, which can occasionally occur even with five fraction regimens and a slightly attenuated dose, as seen above. In turn, we did not note any grade 3 or higher acute or late toxicity in our series, which is potentially a result of choosing slightly less aggressive dosing regimens. As is the case with all retrospective series, one must interpret the results presented here with the appropriate amount of caution. Such studies are subject to an inherent selection bias. In addition, for patients that have died, a cause of death is not always known, making it impossible to guarantee that there was no grade 4–5 toxicity.

The results of the present study provide further evidence that SBRT can be safely delivered to central lesions within the lung, yielding excellent local control. Care must still be taken when choosing the prescription dose, as seen by a higher rate of progression with lower BED_{10}. The final results of RTOG 0813 will provide high level evidence, which will help further guide treatment decisions when approaching this frail patient population with centrally located lung tumors.

Disclosure

No authors report any conflict of interest.

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