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Research Article

Clinical and Radiologic Toxicity after Thoracic Stereotactic Body Radiation Therapy

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Abstract

Purpose

Knowledge about treatment-related toxicity of stereotactic body radiotherapy to the lung is still limited. We conducted a retrospective review of patients treated with stereotactic radiotherapy at our institution to determine the incidence of clinical and radiologic toxicity and their correlation with dosimetric parameters.

Materials and Methods

We analyzed the records of 58 patients who received stereotactic radiotherapy to 73 lung lesions between 1999 and 2008. Fractionation schemes ranged from 3 x 7-20 Gy to 6 x 5 Gy (median biologically equivalent dose 113 Gy, range: 36 – 180 Gy). Medical records were reviewed for assessment of clinical toxicity. Radiologic abnormalities on post-treatment CT scans were graded by two radiologists with the same standard.

Results

Of the 58 patients, the median clinical follow-up was 6.6 months (range: 0 –79.2 months), the median radiologic follow-up for the 73 lesions was 6.4 months (range: 0 – 78.8 months). High-grade clinical toxicity developed in 18 patients, high-grade radiologic toxicity in 44 lesions. A decrease in the incidence of high-grade clinical toxicity correlated with lung V_{20Gy} ≤7% (p=0.05), and radiologic toxicity was closely related to tumor location (p=0.0001). Patients with centrally located tumors developed both high-grade clinical and radiologic toxicity earlier than peripheral lesions (p = 0.03 for clinical and 0.002 for radiologic toxicity), as did those with a high lung V_{20Gy} (p = 0.03 for both clinical and 0.02 for radiologic toxicities). The planning target volume size demonstrated a borderline significant correlation with the development of high-grade clinical toxicity (p = 0.07), smoking status with radiologic toxicity (p=0.06). Incidence and time to development of radiologic and clinical toxicities were associated.

Conclusions

Clinical and radiologic toxicity is a common finding after treatment with thoracic stereotactic radiotherapy. Among the patients who received thoracic SBRT, for the analyzed parameters, lung V_{20Gy} and tumor location were closely related to high-grade clinical and radiologic toxicity-free survival. These parameters can be used to guide treatment and patient follow up.

Keywords: Lung Cancer; Stereotactic Body Radiation Therapy; Clinical Toxicity; Radiologic Toxicity

Abbreviations:

BED: Biologically Equivalent Dose;
COPD: Chronic Obstructive Pulmonary Disease;
GTV: Gross Target Volume;
KPS: Karnofsky Performance Status;
MV: Megavoltage;
NSCLC: Non Small Cell Lung Cancer;
PFT: Pulmonary Function tests;
PTV: Planning Target Volume;
SBRT: Stereotactic Body Radiation Therapy

Introduction

Stereotactic body radiotherapy [SBRT] has been increasingly used to treat patients with early stage non small cell lung cancer [NSCLC] [1-5]. Recent literature consistently reports excellent two to three year local control rates ranging from 88-100% [6-13]. Survival rates in these studies range from 43-65%, similar to outcomes after definitive surgical management in early stage disease. In the published data on SBRT a wide variety of fractionation schemes have been used, thus making the optimal total dose and treatment scheme required for disease control unclear [3-4, 14-16]. However, Onishi et al. [3] found improved local control and survival rates when biologically equivalent dose [BED] was at least 100 Gy [17].

Despite the growing literature on local control and survival for early-stage lung cancer patients, toxicity outcome data is limited. Several SBRT studies have shown a wide range of clinical toxicity, ranging from 0 to 28% [1, 3, 4, 6, 10-12, 16, 18]. Radiologic toxicity is a common finding after SBRT, though the literature on this topic is further limited than for clinical toxicity. Asymptomatic radiologic changes after SBRT can occur in up to 60-100% of patients [19-20]. There is no dose-dependency data with respect to the radiologic outcomes. An especially challenging aspect of interpretation of the available data on radiologic toxicity is the lack of a standard classification system. Though some data has documented the radiographic response after SBRT, a correlation between clinical and radiologic toxicity so far has not been performed [19, 21-22]. Given the paucity of data on clinical and radiologic toxicity, we sought to explore our institution's experience with SBRT. A wide variety of fractionation schemes and total doses have been utilized during approximately ten years of experience, thus allowing for insight on the relationship of dose and toxicity. Both central and peripheral lesions were included. Radiologic toxicity on post-treatment CT scans of the chest was assessed by two attending thoracic radiologists who were blinded to the treatment parameters and clinical outcomes. The primary objective was to determine the incidence of clinical and radiologic toxicity, correlate both types of toxicity, and identify predictive factors to assist clinicians in guiding treatment planning to limit toxicity.

Materials and Methods

A retrospective analysis was conducted of all patients who received thoracic stereotactic radiotherapy in our institution between April 1999 and December 2008. The study was approved by the local Institutional Review Board. Fifty eight sequential patients with 73 lesions were included.

Fourteen patients had more than one lung lesion treated. Thirty-two lesions were metastatic from other sites including cancers of the breast, sarcoma, kidney, colon, esophagus, rectum, liver, melanoma, head and neck, or unknown primary. Forty-one lesions were biopsy-proven primary lung cancers. Twelve lesions were centrally located based on their proximity to the bronchial tree, as previously described in the literature [23]. A variety of fractionation schemes were used, including 3 fractions of 7-20 Gy, 4 fractions of 8-12.5 Gy, 5 fractions of 8-12.5 Gy, and 6 fractions of 6 Gy. The BED, using an alpha/beta ratio of 10 Gy, ranged from 36-180 Gy. The median BED for all lesions was 113 Gy, 66 Gy for central lesions (range: 43-180 Gy), and 113 Gy for peripheral lesions (range: 36-180 Gy); a lower total dose was frequently used for central lesions to limit toxicity. All treatments were delivered using a linear accelerator with 6 and 18 Megavoltage [MV] photon beams. The median planning target volume was 43.5 cm^3 (range: 8.0 – 285.7 cm^3). After radiation treatment delivery, patients were seen in clinical follow-up approximately every three months with a diagnostic chest CT scan at each visit.

Clinical information and therapy data were collected from the medical records including the patients' age, gender, Karnofsky Performance Status [KPS], smoking history, Pulmonary Function Tests [PFT], and pre-treatment oxygen requirement. Oncologic data was also gathered including tumor pathology, radiation fractionation scheme, end of treatment date, prior chemotherapy, prior surgery, prior radiation therapy, tumor site, and pre-treatment dimensions. For two patients, the dosimetric plans were unavailable; therefore, several of their parameters were unknown. See Table 1 for additional patient and treatment characteristics. Local tumor control was assessed on CT findings and, if available, PET/CT or biopsies.

Table 1. Patient and lesion characteristics.

Patient Age	
Median (range)	67 (35 – 83)
Gender (n = 58)	
Male	31
Female	27
Smoking History (n = 58)	
Yes	43
No	10
Unknown	5

Pretreatment oxygen requirement (n = 58)	
Yes	8
No	35
Unknown	15
Number of lesions treated per patient (total 73)	
One	44
Two	13
Three	1
Biologically Equivalent Dose (BED)	
Median (range)	113 Gy (36 – 180 Gy)
≤ 60 Gy	13
60 – 80 Gy	10
80 – 100 Gy	6
100 – 120 Gy	32
>120 Gy	11
BED for Central Tumors (n=12)	
Median (range)	66 Gy (43 – 180 Gy)
BED for Peripheral Tumors (n=61)	
Median (range)	113 Gy (51 – 180 Gy)

Clinical toxicity symptoms were graded per the "Subjective" and "Management" portion of the LENT-SOMA scale. The incidence and time to development of clinical toxicity, from the end of radiation treatment date, were also noted. Subsequently, the patients were subcategorized into low (Grades 1 and 2) and high-grade (Grades 3 and 4) clinical toxicity groups.

To assess incidence and time to radiologic toxicity, 2 attending thoracic radiologists analyzed pretreatment and all available post-treatment chest CT scans including scans obtained at outside locations. Each CT scan was graded with the "Objective" portion of the LENT-SOMA scale [19]. Grade 1 and 2 represented low-grade radiologic toxicity, grade 3 and 4 were interpreted as high-grade radiologic toxicity. The radiologists worked together to generate a consensus score for each post-treatment CT scan for each patient. A total of 165 scans (median of 3 scans per patient, range 1-12) were reviewed. Radiologists were only provided with limited patient information including the patient's medical record number, which lobe of the lung was treated with radiotherapy and the end of radiation treatment date. Radiologists were blinded to fractionation scheme, dosimetric parameters, treatment outcomes, and clinical toxicity.

Potential relations between clinical and radiologic toxicities and smoking status, target size and location (peripheral versus central), as well as dosimetric parameters (BED, lung V_{20Gy} and V_{5Gy} (the percentage of the lung volume receiving at least 20 Gy and 5 Gy, respectively)) were investigated.

Statistical analysis

Statistically significant association of the above mentioned factors on clinical and radiologic toxicity was analyzed using a time-to-event model. Each of the 58 patients was represented with one lesion and the event was defined as occurrence of toxicity based on the type of toxicity. Local control and time-to-toxicity probabilities were estimated using Kaplan-Meier survival function. Differences were tested using a log-rank test. The influence of covariates on toxicities was tested using a Cox-proportional hazards model. All tests were assumed significant at a 5% level. Software R v2.13 was used for testing.

A separate time-to-event analysis was done with the event defined as first occurrence of high-grade radiologic toxicity, low-grade clinical toxicity or high-grade clinical toxicity. The correlation of clinical and radiologic toxicities was explored by a chi-square test for incidence and by stochastic ordering using a pairwise plot of time to the different toxicities. A pairwise t-test was used to assess statistically significant differences.

Results

Follow up

Of the 58 patients, the median clinical follow-up was 6.6 months (range: 0 – 79.2 months). The median radiologic follow-up for the 73 lesions was 6.4 months (range: 0 – 78.8 months).

Clinical toxicity

Low-grade clinical toxicity was noted in 17 of the 58 patients (29%), 5 patients with central lesions and the remaining in patients with peripheral lesions. High-grade clinical toxicity was noted in 18 of the 58 patients (31%), 3 central locations, and the remaining were patients with peripheral tumors. The most common low-grade clinical toxicity was cough; other symptoms included fatigue, wheezing, mild dyspnea on exertion, mild skin fibrosis, in-field erythema/hyperpigmentation, musculoskeletal pain in the region of treatment controlled with over the counter medications. The most frequent high-grade clinical toxicity was chest wall pain necessitating narcotics for pain control and/or physical therapy; other symptoms included dyspnea requiring steroids and/or hospitalization, lymphedema, a new oxygen requirement, rib fracture, and tracheostomy placement.

The median time to low-grade clinical toxicity was 3 months (range: 0.5 – 39.1 months); the median time to high-grade clinical toxicity was 5.3 months (range: 0.1 – 41.6 months). Clinical toxicity developed earlier in centrally located tumors ($p = 0.005$ for low grade and $p = 0.03$ for high grade toxicities) and high lung V_{20Gy} ($p = 0.03$). Results were borderline significant

for larger Planning Target Volumes [PTV] (p=0.07). BED (p = 0.29), V_{5Gy} (p = 0.17), and smoking status (p = 0.68) were not related to the development of clinical toxicity. Patients with a V_{20Gy} ≤ median value of 7% had an increased rate of high-grade toxicity-free survival (p = 0.05, Figure 1).

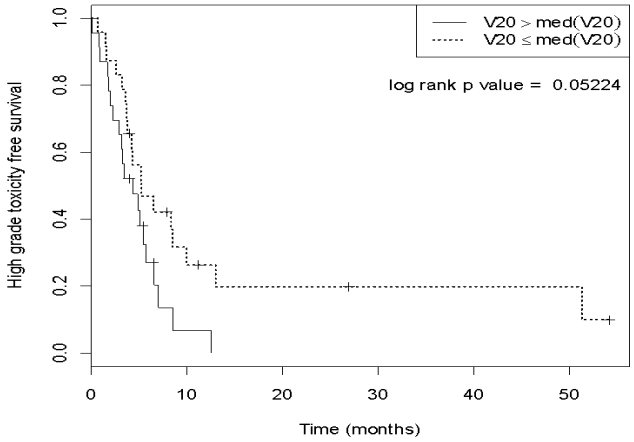

Figure 1. Correlation of V_{20Gy} with High Grade Clinical Toxicity Free Survival.

Radiologic toxicity

High-grade radiologic toxicity was observed in 44 of 73 lesions (60%) in 36 patients. Of the 44 lesions, 11 were central and 33 were peripheral. The median time to the development of high-grade radiologic toxicity was 6.3 months (range: 0.7-51.3 months).

High-grade radiologic toxicity developed earlier in larger lung V_{20Gy} (p = 0.02), central tumor location (p = 0.002), and in smokers (p = 0.06). BED (p = 0.11), lung V_{5Gy} (p = 0.43), and PTV (p = 0.12) were not significantly related to the development of radiologic toxicity. High-grade radiologic toxicity free survival was higher in peripheral lesions (p=0.0001, Figure 2).

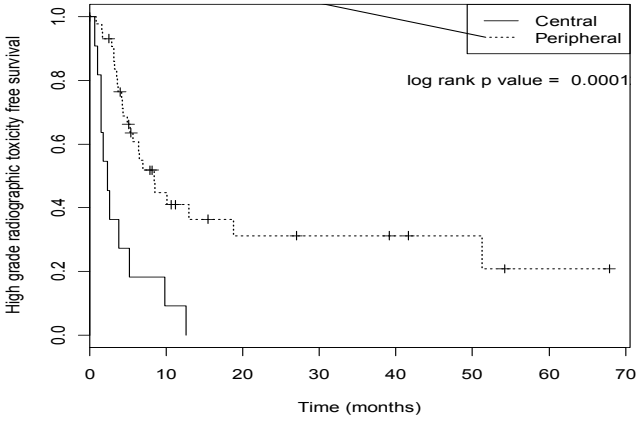

Figure 2. Correlation of Tumor Location with High Grade Radiologic Toxicity Free Survival.

Relation between clinical and radiologic toxicity

Of the 36/58 patients that developed high grade radiologic toxicity, 13 patients had high-grade clinical toxicity. The incidence of radiologic and high grade clinical toxicity was not significantly different (p=0.4).

A comparison between time to high-grade radiologic and clinical toxicity was performed using a pairwise plot of time (Figure 3; only those patients with radiologic toxicity were included). The median time to development of low grade clinical toxicity was 6.8 months and 8.1 months for high grade clinical toxicity in the radiologic toxicity subgroup, indicating that the time to appearance of toxicity was not different for radiologic and clinical toxicity (p=0.6).

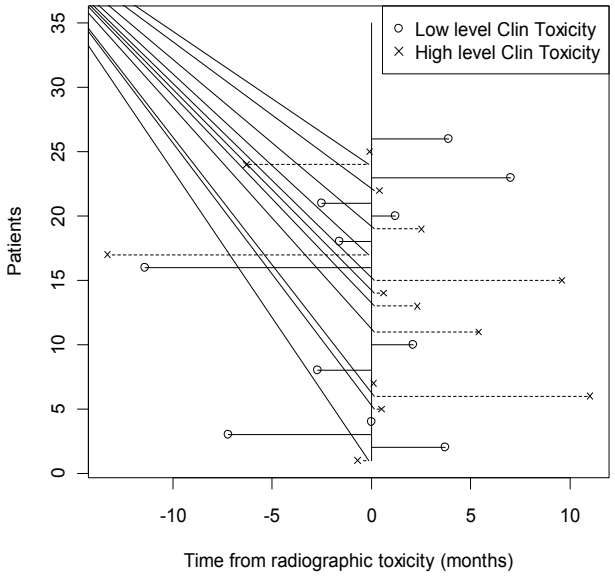

Figure 3. Correlation of Clinical and Radiologic Toxicity.

Discussion

This retrospective analysis represents a review of our institution's experience with SBRT using various fractionation schemes over a period of nearly ten years. We found an incidence of 60% high-grade radiologic toxicity, 29% low-grade clinical toxicity, and 31% high-grade clinical toxicity. Ninety-one percent of central tumors developed high-grade radiologic toxicity versus 54% of peripheral tumors. There was no significant correlation between any toxicity and BED, PTV size, smoking history, or lung V_{5Gy}.

Clinical toxicity, tumor size and tumor location

Sampson performed a literature search between 1995 and 2005 for stereotactic body radiation therapy of the lung and/or liver to study treatment safety (20). Of the fifteen lung stud-

ies and 683 patients, the incidence of grade 1-2 toxicity was up to 8%, grade 3-5 toxicity was up to 15%, and treatment-related mortality was 0.3%. These estimates are much lower than in our study, where the incidence of low and high grade clinical toxicity was 29% and 31%, respectively; however, it is important to note that there was no standardized grading scale used in the reviewed literature. Sampson found no association between toxicity and radiation dose, though a probable relationship was found between the radiation treatment volume and toxicity. A group in Germany performed a retrospective analysis of 59 patients consecutively treated between 2005 and 2008 with lung SBRT [1]. Thirteen patients had either two or three pulmonary metastases treated. There were 58 peripheral lesions and 17 central lesions. A risk-adapted fractionation protocol was used for central tumors and/or larger tumor volumes. Only clinically symptomatic radiation pneumonitis requiring treatment was scored as an endpoint in this study (i.e. SWOG toxicity criteria ≥ grade 2). After a median follow-up of 13 months, grade 2 pneumonitis was seen in 11 of 59 patients (19%); no patients had a new oxygen requirement (SWOG grade 3). The median time to development of pneumonitis was 5 months which is comparable to the development of toxicity in our study (3 and 5.3 months). Low grade clinical toxicity was 29% in our study with the majority being increased cough.

In Timmerman's phase II study [23], 70 patients with medically inoperable T1-T2N0 NSCLC were enrolled; there was no restriction with respect to tumor location. 83% of the patients developed Grade 1-2 clinical toxicity, 11% of these patients experienced Grade 3-4 toxicity. The median time to toxicity was 7.6 months. For patients who experienced high-grade toxicity (grade 3 to 5), tumor location (hilar/pericentral versus peripheral) was a significant predictor of toxicity ($p = .004$). The 2-year freedom from severe toxicity was 83% for peripheral tumors and 54% for perihilar/central tumors. Gross tumor volume [GTV] size was found to be a significant predictor of grade 3 to 5 toxicity; there was an eight-fold risk of high-grade toxicity for tumors with GTV volume > 10 mL ($p = 0.017$). Although time to development of high grade clinical toxicity was similar in our study, we noticed a higher incidence of high grade clinical toxicity in 31% of our patients. Central tumor location was significantly associated with lower radiologic toxicity-free survival in our study. In addition, a decreased local recurrence-free survival in patients with central tumors was observed. This is potentially due to the reported correlation between central tumors and toxicity leading to a lower median dose delivered in an effort to reduce toxicity. Similar to Timmerman et al. [23] and Guckenberger et al. [1], tumor size (i.e. PTV) predicted for clinical toxicity.

As experience with SBRT grows, research has been exploring how to use this treatment modality for tumors previously considered untreatable. A group at The University of Texas MD Anderson Cancer Center retrospectively reviewed their experience with centrally located early stage or isolated NSCLC recurrences [24]. The most common fractionation scheme was 50 Gy in 4 fractions; if the predetermined dose constraints could not be met, 70 Gy would be delivered in 10 fractions. With a median follow-up of approximately 2.5 years, no patients developed grade 4 or 5 toxicity; however, the incidence of grade 1 chest wall pain was 18% and 11% had grade 2 radiation pneumonitis. Several parameters were identified as independent predictors of pneumonitis, including a mean total lung dose >6 Gy, V_{20Gy} >12%, and the ipsilateral V_{30Gy} >15%.

Radiologic toxicity

Similar to clinical toxicity rates, the true incidence of radiologic toxicities is not clear which is partly due to the use of a variety of scoring schemes and subjective interpretation. A Dutch group retrospectively analyzed their patients treated with SBRT for stage I NSCLC between 2003 and 2008 [25]. Three thoracic radiation oncologists generated a consensus score for all follow-up chest CT scans based on degree of consolidation or ground glass opacity for acute toxicity, or degree of fibrosis for late toxicity. After a median follow-up of 2.5 years, nearly all patients developed some radiographic changes which continued to evolve over time after treatment. The authors emphasized the importance of differentiating these expected changes with signs of local failure.

At Princess Margaret Hospital, six thoracic Radiation oncologists all utilized a four-category stratification tool to classify post-SBRT chest CT findings to evaluate interrater variability [26]. The categorization scheme was found to have some limitations, including experience with the scoring tool, and further development of an alternative method was recommended. To avoid a bias in image interpretation in our review, two specialized thoracic radiologists read all CT scans in consensus using the LENT-SOMA scale [27] for grading radiologic toxicities. Our study had an incidence of high-grade radiologic toxicity of 60% which is lower than other reports where radiologic toxicity is observed in all SBRT patients. The incidence of high-grade radiologic toxicity was essentially the same as the incidence of combined low and high-grade clinical toxicity.

While a comparable incidence of clinical and radiologic toxicity supports the use of an existing scoring system, more detailed descriptions of early groundglass and consolidation changes and variations of late fibrosis on post therapy CT images have been proposed [28]. A Japanese group correlated clinical pneumonitis with CT radiologic changes and found significant correlations using a descriptive system of radiologic changes that has also been used for conventionally fractioned radiotherapy [29]. Our study demonstrated that both the time to toxicity and the incidence are comparable for clinical and radiologic toxicities.

While the retrospective nature of our study limits the strength of our findings, the evaluation of consecutive patients and the independent CT image review by two radiologists supports the validity of our results. The sample size, although small, is comparable or higher than similar studies on SBRT toxicity. The median follow-up in our study is similar to the expected time to the development of toxicity as confirmed by other above mentioned reports, thereby indicating a sufficient length of observation after treatment.

Conclusion

Both clinical and radiologic toxicities are frequently observed after lung SBRT with the incidence and time to development of both types of toxicities being similar. A lung V_{20Gy}≤7% predicted for improved clinical toxicity-free survival, peripheral tumor location predicted for improved radiologic toxicity-free survival. Further investigations are needed to confirm the findings presented in this study.

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