Low Toxicity for Lung Tumors Near the Mediastinum Treated with Stereotactic Body Radiation Therapy (SBRT)

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Purpose: To report the local control, survival and low toxicity observed at the Cooper University Hospital CyberKnife Center post SBRT in the treatment of lung tumors near the mediastinum.

Methods and Materials: Twenty four medically inoperable lung cancer patients with tumors near the mediastinum were treated using the Accuray CyberKnife system (Accuray, Sunnyvale, CA) with Monte Carlo dose calculations and heterogeneity corrections from July 2008 to May 2010. The prescription dose ranged from 28.5 Gy to 60 Gy in three to five fractions. For conventional fractionation schemes Emami organized the dose tolerance limits into a unified format for clinical utility and partitioned them into two risk levels (5% and 50%) with pre-set volumes for most critical structures throughout the body. In contrast, statistical SBRT dose tolerance limits for mediastinal structures have not been established yet. We have sufficient experience at least to begin organizing a unified format with low-risk and high-risk partitions and pre-set volumes for 1-5 fractions exposing mediastinal structures. With the help of the DVH Evaluator, a software tool developed by our senior author, each treatment plan was assessed for safety and feasibility prior to treatment. The DVH Evaluator was also used to analyze the followup data and to create graphs of risk, called DVH Risk Maps, superimposing clinical data onto the unified SBRT dose tolerance limits.

Results: It was not feasible to prescribe the doses of peripheral lung lesions for all tumors near the mediastinum because of known toxicity. The crude local tumor control rate achieved in our series was 92%. Five of the 15 primary non small cell lung cancer patients developed distant metastasis, and six of the 9 metastatic lung patients developed additional distant metastasis. Median survival was 26.8 months for the primary lung cases and 9.6 months for the metastatic cases. None of the 24 patients experienced Grade 3 or higher toxicities.

Conclusions: We affirm that SBRT is feasible in the treatment of centrally located lung cancers when the dose tolerance limits of critical structures are diligently respected. The low adverse event rates that we have experienced combined with a good local tumor control rate is encouraging.

Key words: Dose tolerance limits; Adverse events; Stereotactic body radiotherapy; Radiosurgery; DVH Evaluation

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Conflicts of interest: None of the authors has received any funding for this research. The senior author developed the DVH Evaluator software tool which is an FDA-cleared product in commercial use. This research is authorized by Cooper University Hospital Institutional Review Board protocol #10-094EX.

Note: The senior author is now at Holy Redeemer Hospital, 1648 Huntingdon Pike, Meadowbrook, Pa 19046

INTRODUCTION

Stereotactic body radiation therapy (SBRT) in patients with inoperable early stage non-small cell lung cancer has resulted in promising local control and survival with low toxicity for peripheral lesions (1). Although local control rates in excess of 97% have been published in the literature for peripheral lung tumors treated with SBRT (2), treatment of lung tumors near the mediastinum remains a therapeutic challenge. Excessive toxicities including adverse events (AE) as high as Grade 5 (i.e., death) have resulted (3, 4) when the SBRT dose fractionation schedules for peripheral lesions have been used near the mediastinum.

Since the tumor proximity to critical mediastinal structures is the major dose limiting factor their dose tolerance limits need to be diligently studied. The ongoing RTOG 0813 protocol (5) is exploring potentially safer 5-fraction treatment regimens for small (<5 cm) centrally located non-small cell carcinoma lung cancers (5).

While awaiting the long-term statistical protocol results, we analyzed the available data and organized over 100 published dose tolerance limits of critical mediastinal structures, and present them in a unified format to assist the clinician in analyzing the safety and efficacy of prescribed doses. We report the clinical results from 24 patients with lung tumors near the mediastinum that were treated with SBRT at Cooper University Hospital (CUH). Primary endpoints of this study were local control, median survival and treatment related toxicities.

Nguyen et al. summarized a number of studies of SBRT patients with early stage lung cancer who received biological equivalent doses (BED) of 100 Gy_{10} or more (6), where Gy_x denotes $x=\alpha/\beta$ in the linear quadratic model. Three of the studies that Nguyen cited reported five-year survival ranging from 30% to 83%. The largest series of 257 patients with stage I non small cell lung cancer demonstrated a significant local control and survival advantage when a BED of 100 Gy_{10} or higher was delivered (7).Whenever feasible we used a prescription dose with BED of

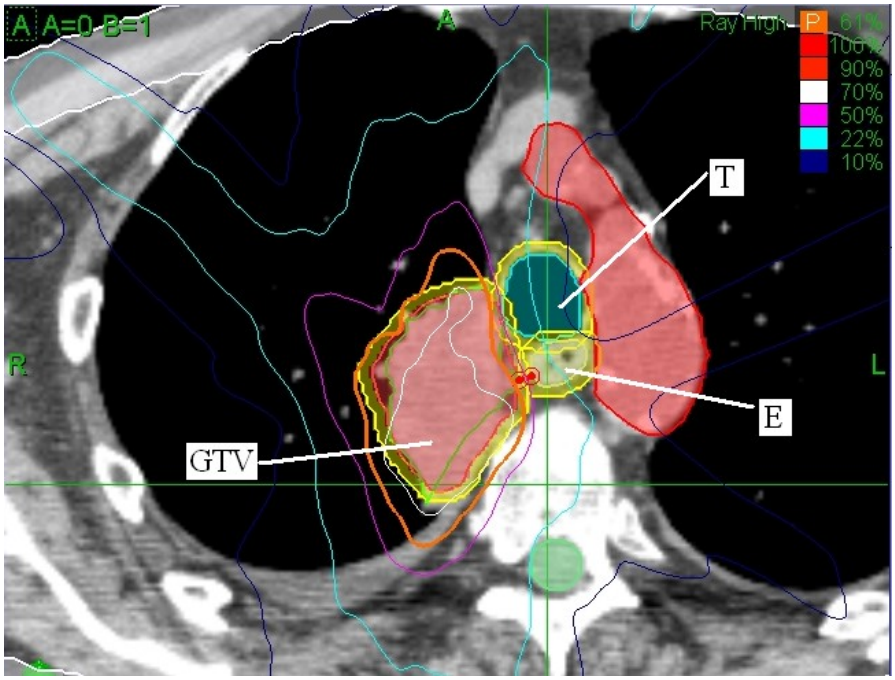


Figure 1. Right mediastinal lung sample case, with gross tumor volume (GTV) near trachea (T) and esophagus (E).

100 Gy_{10} or higher, but for many mediastinal cases the proximity of critical structures and the uncertainty of the dose tolerance precluded the use of such a dose.

Timmerman's prospective trials using SBRT in North America have identified potent dose levels and confirmed their efficacy, but noted that excessive toxicity had been observed for some patients with tumors near the central airways (3). Patients with clinical stage I disease at or encroaching on the mediastinum remain a therapeutic challenge because of reported treatment related toxicities from normal organs when given the same dose and fractionation schedule with SBRT as the peripheral lesions. Until statistically proven dose tolerance limits are established we at CUH continue to seek alternate prescription strategies to avoid toxicity.

METHODS AND MATERIALS

Eligibility

From the CUH Department of Radiation Oncology CyberKnife database, all 24 medically inoperable lung cancer patients with tumors near the mediastinum that were treated with SBRT between July 2008 to May 2010 that had Monte Carlo dose calculations with heterogeneity corrections were analyzed. The 24 patients had 25 lesions, which were either primary early stage (T1-2N0M0) or metastatic, less than 5 cm in diameter, and near mediastinal structures. They were consented for treatment and retrospectively evaluated in accordance with CUH Institutional Review Board protocol #10-094EX. Both primary and metastatic lesions had pathological confirmation whenever clinically indicated. Fifteen of the 24 patients had primary lung tumors whereas 9 were metastatic. Prior to treatment, PET-CT and diagnostic CT imaging with or without contrast was performed as clinically indicated. Patient characteristics are listed in Table 1 and a representative case study is shown in Fig. 1. Patient ages ranged from 37 to 87 years with median of 73 years; 11 patients were male and 13 were female; 18 were white (Non-Hispanic) and 6 were African American.

Treatment Characteristics

The course of treatment for the patients ranged from three to five fractions delivered in three to eighteen days (two to seventeen elapsed days) with only two exceeding eleven elapsed days, and the median number of elapsed days was four. Rather than rigidly prescribing the same dose for all cases, the physicians carefully assessed the risk/benefit ratio for each patient, based on the anatomical proximity to critical structures and the current understanding of the dose tolerance and the dose required to achieve the desired therapeutic outcome.

We used a dosimetric definition of mediastinal tumor. Any tumor treated with SBRT within 2 cm of the bronchial tree would most certainly approach at least one of the low-risk dose tolerance limits of a critical mediastinal structure. However, with the high doses used in SBRT it is possible for tumors more than 2 cm away from the bronchial tree to result in doses with the same level of increased risk to mediastinal critical structures. For this reason, we defined a mediastinal tumor to be any tumor that has a treatment plan within 5 Gy or 5% of the low-risk SBRT dose tolerance limits of the critical structures aorta, bronchi, esophagus, heart, and trachea. Some of the cases in this study were directly against these mediastinal critical structures

but had not invaded them and others were more than 2 cm away yet still contributed a high dose to the mediastinum.

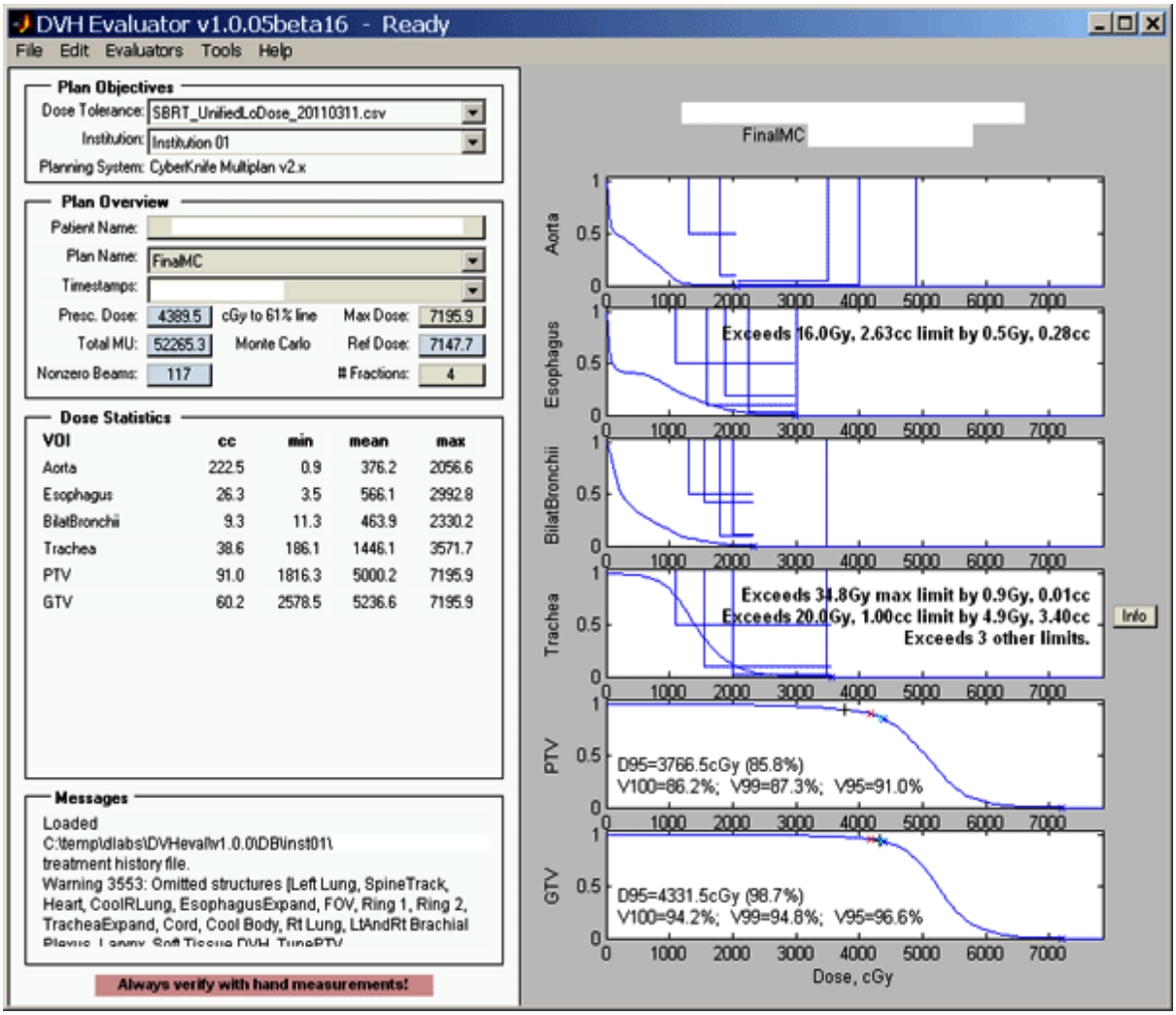


Figure 2. DVH Evaluator analysis for a sample patient. The curved lines represent the patient's dose-volume histogram (DVH) for each anatomic structure; the horizontal and vertical lines represent the volume and dose of the tolerance limits, respectively, and the space between the DVH and the limits shows the margin of safety. The boldface text shows explicit numerical warnings whenever limits are exceeded; if too many limits are exceeded to display, the rest are available via the popup Info box.

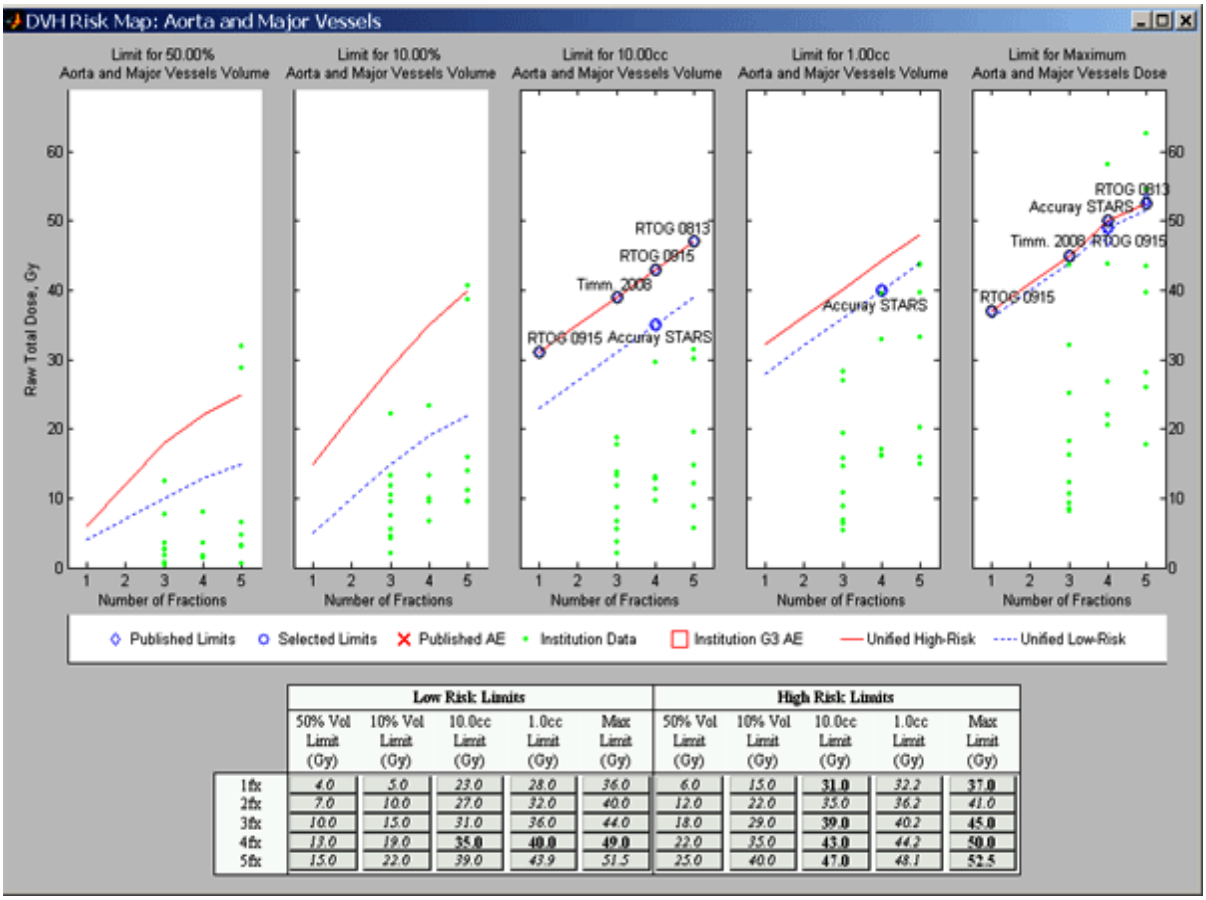
DVH Evaluation

The DVH Evaluator is an FDA-cleared product that is distributed by LifeLine Software (Austin, Tx) and was developed by the senior author. In our institution we use the DVH Evaluator to assess each CyberKnife plan with respect to the dose tolerance limits prior to treatment, as shown in Fig. 2. Since new SBRT dose tolerance limits continue to be published on a monthly basis, the choice of which limits to apply can be easily selected from a drop-down list in the user interface. The DVH Evaluator also archives aggregate data for analysis and can generate the DVH Risk Maps as shown in Figs. 3-7 for the mediastinal critical structures aorta, bronchi, esophagus, heart and trachea. The DVH Risk Maps summarize much of the available

clinical data in both graphical and tabular form to facilitate clinical decision making. All published dose tolerance limits are plotted as blue diamonds; the published limits that we selected as low-risk and high-risk representatives for our institution are plotted as blue circles; any published adverse events are plotted as red X's; the doses actually delivered to the critical structures of our patients are plotted as green dots; if there had been any Grade 3 or higher adverse events in our institution they would have been plotted as red squares; the linearly interpolated/extrapolated low-risk trend is plotted as a blue line and the corresponding high risk trend is plotted as a red line. The **boldface** doses in the tabular portion of Figs. 3-7 are the selected published expert opinion dose tolerance limits, and the *italicized* doses are linearly interpolated/extrapolated to fill the gaps.

Table 1. Characteristics of treatments

Case #	Rx Dose	Rx Isodose Line	Num Fx	BED Gy_{10}	2 Gy_{10} Equiv.	Elapsed Days	GTV cc	PTV cc
1	36	81%	3	79.2	66	2	44.3	105.1
2	40	60%	5	72	60	6	121	217.9
3	54	77%	3	151.2	126	2	2.4	11.7
4	44	61%	4	92.4	77	11	60.2	91
5	60	66%	3	180	150	2	31.3	64.6
6	50	71%	4	112.5	93.8	7	16.9	31.2
7	54	75%	3	151.2	126	2	24.3	49.2
8	60	77%	3	180	150	2	12.3	33
9	28.5	60%	3	55.6	46.3	10	18.9	47.9
10	60	80%	3	180	150	2	2.5	11.1
11	60	65%	3	180	150	5	2.8	14.2
12	32.5	60%	5	53.6	44.7	8	34.5	49.7
13	54	60%	4	126.9	105.9	4	2.5	10
14	54	70%	3	151.2	126	2	12.3	34.5
15	45	60%	4	95.6	79.7	11	32.8	76.7
16	32.5	65%	5	53.6	44.7	4	67.9	123.3
17	54	63%	3	151.2	126	4	8.7	24.1
18	50	61%	5	100	83.3	6	12.3	37.8
19	54	82%	3	151.2	126	2	19.3	45.4
20	60	74%	3	180	150	2	22.6	53.3
21	60	74%	3	180	150	2	24.4	54.8
22	32	67%	4	57.6	48	8	63.7	119.6
23	45	71%	3	112.5	93.8	14	53.4	101.4
24	45	77%	3	112.5	93.8	2	72.9	133.2
25	54	70%	5	112.3	93.6	17	22.7	45.5
min	28.5	60%	3	53.6	44.7	2	2.4	10
median	54	70%	3	112.5	93.8	4	22.7	49.2
mean	48.7	69%	3.6	102.4	102.4	5.5	31.5	63.4
max	60	82%	5	180	150	17	121	217.9



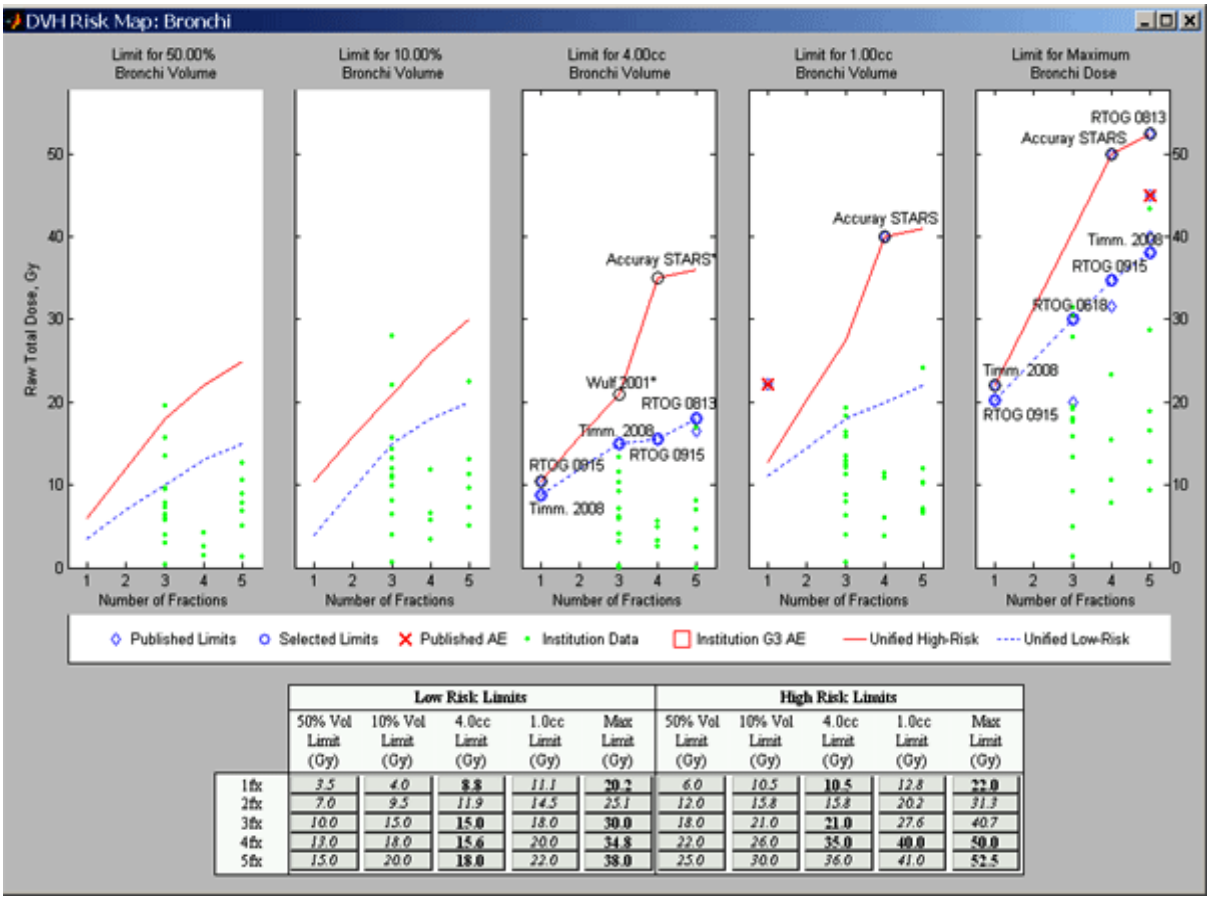
	Low Risk Limits					High Risk Limits				
	50% Vol Limit (Gy)	10% Vol Limit (Gy)	10.0cc Limit (Gy)	1.0cc Limit (Gy)	Max Limit (Gy)	50% Vol Limit (Gy)	10% Vol Limit (Gy)	10.0cc Limit (Gy)	1.0cc Limit (Gy)	Max Limit (Gy)
1fx	*4.0*	*5.0*	*23.0*	*28.0*	*36.0*	*6.0*	*15.0*	**31.0**	*32.2*	**37.0**
2fx	*7.0*	*10.0*	*27.0*	*32.0*	*40.0*	*12.0*	*22.0*	*35.0*	*36.2*	*41.0*
3fx	*10.0*	*15.0*	*31.0*	*36.0*	*44.0*	*18.0*	*29.0*	**39.0**	*40.2*	**45.0**
4fx	*13.0*	*19.0*	**35.0**	**40.0**	**49.0**	*22.0*	*35.0*	**43.0**	*44.2*	**50.0**
5fx	*15.0*	*22.0*	*39.0*	*43.9*	*51.5*	*25.0*	*40.0*	**47.0**	*48.1*	**52.5**

Figure 3. DVH Risk Map for aortic toxicity. (Bolded limits are published data and *italicized* are interpolated/extrapolated.)

Unified Dose Tolerance Format

Emami's method (8) to organize conventional dose tolerance limits into a unified format for clinical utility was to use the same percentage volumes (1/3, 2/3, and 3/3) for most critical structures throughout the body, and to partition into two risk levels (5% and 50%). In this manner, Emami's dose tolerance limit table consisted of one row for each critical structure, with six doses in each row; three low-risk (5%) doses and three high-risk (50%) doses, by volume (1/3, 2/3, and 3/3). For SBRT a similar unified format was needed, but due to the strong dependence on fractionation, five rows were needed for each critical structure according to the number of fractions (1-5), and the volumes were much different than for conventional fractionation. For most published SBRT dose tolerance limits the statistical risk is still unknown, so we have just labeled the two partitions of the limits as "low-risk" and "high-risk", and although their risk levels are most likely well below 5% and 50%, we will not know for sure until the long-term statistical results emerge.

The most common published SBRT dose tolerance limits are for the maximum point dose (i.e. zero volume) (9) which is an additional parameter which must be included in the risk factors for SBRT (see the fifth column of each risk group in Figs. 3-7). For the volume limits, the ablative doses of SBRT are only tolerable to a small volume; for each critical structure we chose the two most common cubic centimeter (cc) absolute volumes (columns three and four of each group in



	Low Risk Limits					High Risk Limits				
	50% Vol Limit (Gy)	10% Vol Limit (Gy)	4.0cc Limit (Gy)	1.0cc Limit (Gy)	Max Limit (Gy)	50% Vol Limit (Gy)	10% Vol Limit (Gy)	4.0cc Limit (Gy)	1.0cc Limit (Gy)	Max Limit (Gy)
1fx	*3.5*	*4.0*	**8.8**	*11.1*	**20.2**	*6.0*	*10.5*	**10.5**	*12.8*	**22.0**
2fx	*7.0*	*9.5*	*11.9*	*14.5*	*25.1*	*12.0*	*15.8*	*15.8*	*20.2*	*31.3*
3fx	*10.0*	*15.0*	**15.0**	*18.0*	**30.0**	*18.0*	*21.0*	**21.0**	*27.6*	*40.7*
4fx	*13.0*	*18.0*	**15.6**	*20.0*	**34.8**	*22.0*	*26.0*	**35.0**	**40.0**	**50.0**
5fx	*15.0*	*20.0*	**18.0**	*22.0*	**38.0**	*25.0*	*30.0*	*36.0*	*41.0*	**52.5**

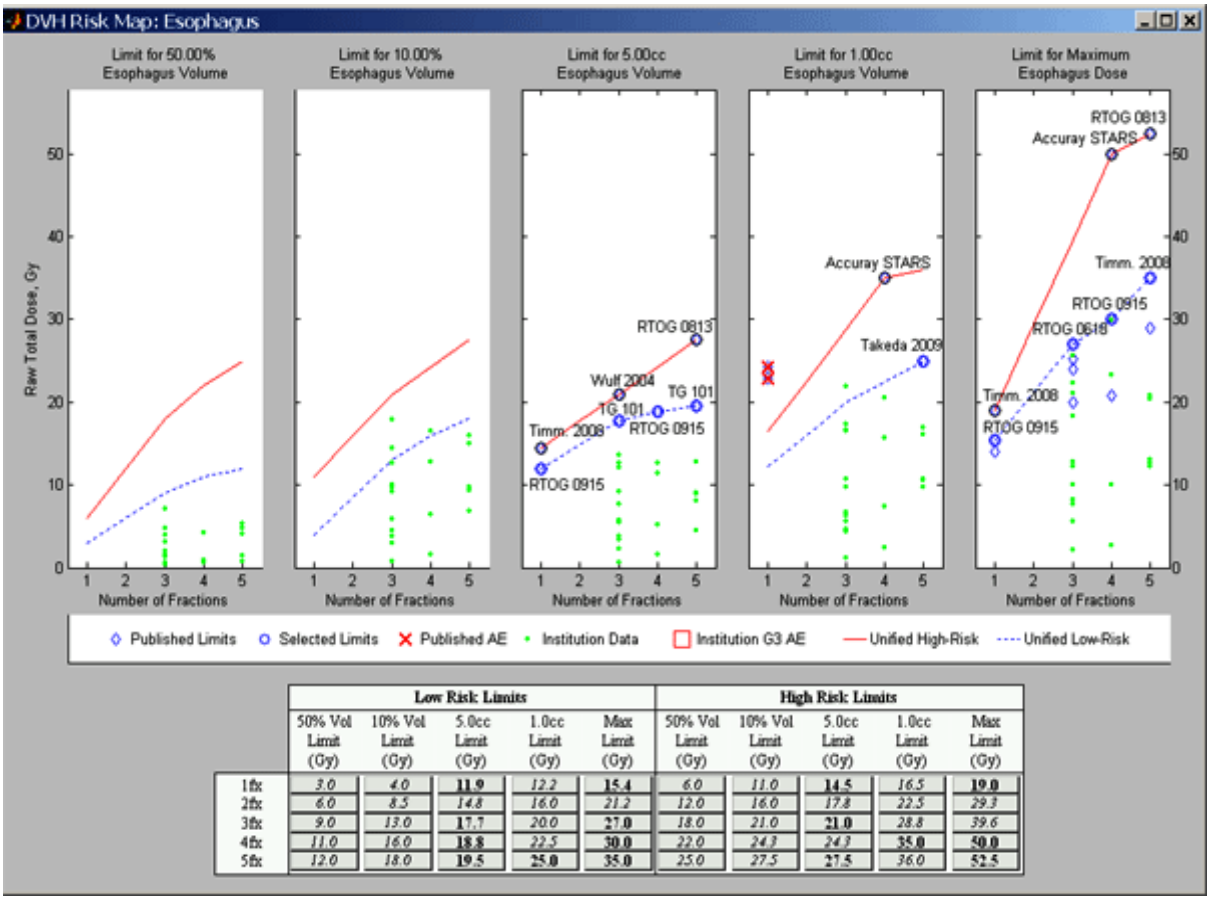
Figure 4. DVH Risk Map for bronchial toxicity. (Bolded limits are published data and *italicized* are interpolated/extrapolated.)

Figs. 3-7). Although the rationale of SBRT dose tolerance limits permits very small absolute volumes to receive ablative doses, such high doses should not be allowed to extend to large volumes of critical structures, hence the large volume percentage limits in columns one and two of each group.

In summary, the unified dose tolerance format for SBRT has five rows, one for each fractionation 1-5; two groups of columns, one for low-risk and one for high-risk; and five columns within each group, for each of the five dose-descriptor points.

Preliminary Unified Dose Tolerance Limits

The following method was used to establish dose tolerance limits in our institution for mediastinal structures: After an extensive literature review of more than 500 SBRT dose tolerance limits (9), about 100 dose limits for the mediastinal critical structures aorta, bronchi, esophagus, heart, and trachea were identified. These were partitioned into the low-risk and high-risk categories by a heuristic algorithm; when possible by the median BED of all the published limits for a given organ. For example, if $\alpha/\beta = 3$, the linear quadratic (LQ) model predicts that the median BED of all the 5 cc dose tolerance limits for esophagus is 59.1 Gy_3 (see Fig. 5). All of the dose tolerance limits above 59.1 Gy_3 were partitioned as high-risk limits and all those below 59.1 Gy_3 were partitioned as low-risk. For the maximum dose esophagus limits, the



	Low Risk Limits					High Risk Limits				
	50% Vol Limit (Gy)	10% Vol Limit (Gy)	5.0cc Limit (Gy)	1.0cc Limit (Gy)	Max Limit (Gy)	50% Vol Limit (Gy)	10% Vol Limit (Gy)	5.0cc Limit (Gy)	1.0cc Limit (Gy)	Max Limit (Gy)
1fx	*3.0*	*4.0*	**11.9**	*12.2*	**15.4**	*6.0*	*11.0*	**14.5**	*16.5*	**19.0**
2fx	*6.0*	*8.5*	*14.8*	*16.0*	*21.2*	*12.0*	*16.0*	*17.8*	*22.5*	*29.3*
3fx	*9.0*	*13.0*	**17.7**	*20.0*	**27.0**	*18.0*	*21.0*	**21.0**	*28.8*	*39.6*
4fx	*11.0*	*16.0*	**18.8**	*22.5*	**30.0**	*22.0*	*24.3*	*24.3*	**35.0**	**50.0**
5fx	*12.0*	*18.0*	**19.5**	**25.0**	**35.0**	*25.0*	*27.5*	**27.5**	*36.0*	**52.5**

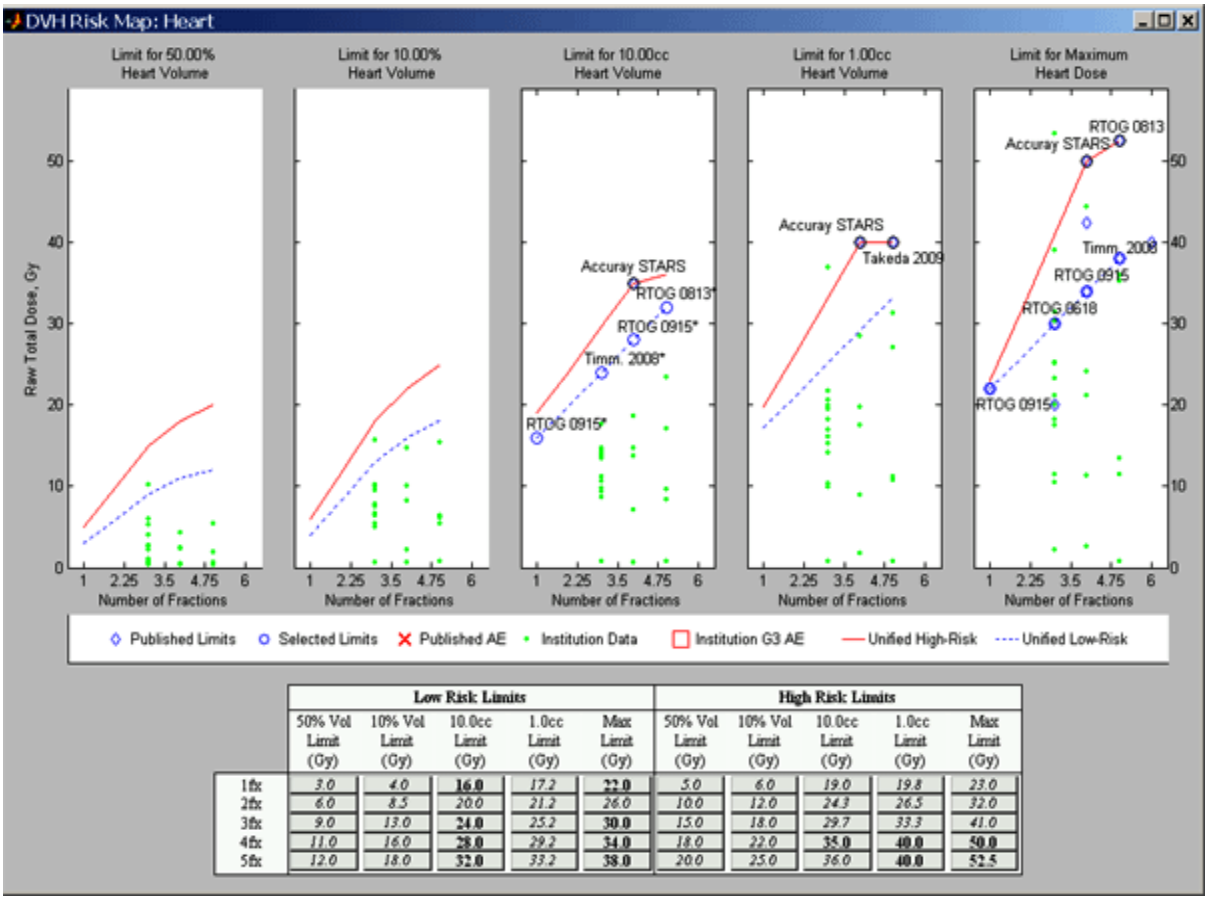
Figure 5. DVH Risk Map for esophageal toxicity. (Bolded limits are published data and *italicized* are interpolated/extrapolated.)

Accuray STARS (10) and RTOG 0813 (5) limits are dramatically higher than all the others. Rather than discarding these points as outliers, we observed that these protocols continue to accrue patients without yet encountering dose-limiting toxicity, so we used these as the high-risk limits for the time being. Two of the published 1 cc dose tolerance levels in Fig. 5 were reported with corresponding adverse events; these may ultimately prove to be acceptable risk levels but for now we have not used these points as dose tolerance limits in our institution. Where insufficient data points were available for 1 cc dose limits, the values were interpolated between the maximum point dose and 5 cc dose tolerance limits, according to an average DVH curve.

Statistical analysis of long term adverse event data will ultimately determine the ideal volumes and doses, but our unified dose tolerance limits have been clinically useful until such data becomes available.

Follow up

Patients were followed with physical examination and PET-CT and or CT imaging approximately every 3 months post treatment. Tumor response was recorded and evaluated as per the RECIST1.1 criterion in which complete response is the complete disappearance of the tumor and partial response is the decrease in the longest tumor diameter by ≥ 30% (11). The RECIST1.1 definition of progressive disease is when the sum of the diameters increased by ≥



	Low Risk Limits					High Risk Limits				
	50% Vol Limit (Gy)	10% Vol Limit (Gy)	10.0cc Limit (Gy)	1.0cc Limit (Gy)	Max Limit (Gy)	50% Vol Limit (Gy)	10% Vol Limit (Gy)	10.0cc Limit (Gy)	1.0cc Limit (Gy)	Max Limit (Gy)
1fx	*3.0*	*4.0*	**16.0**	*17.2*	**22.0**	*5.0*	*6.0*	*19.0*	*19.8*	*23.0*
2fx	*6.0*	*8.5*	*20.0*	*21.2*	*26.0*	*10.0*	*12.0*	*24.3*	*26.5*	*32.0*
3fx	*9.0*	*13.0*	**24.0**	*25.2*	**30.0**	*15.0*	*18.0*	*29.7*	*33.3*	*41.0*
4fx	*11.0*	*16.0*	**28.0**	*29.2*	**34.0**	*18.0*	*22.0*	**35.0**	**40.0**	**50.0**
5fx	*12.0*	*18.0*	**32.0**	*33.2*	**38.0**	*20.0*	*25.0*	*36.0*	**40.0**	**52.5**

Figure 6. DVH Risk Map for cardiac toxicity. (Bolded limits are published data and *italicized* are interpolated/extrapolated.)

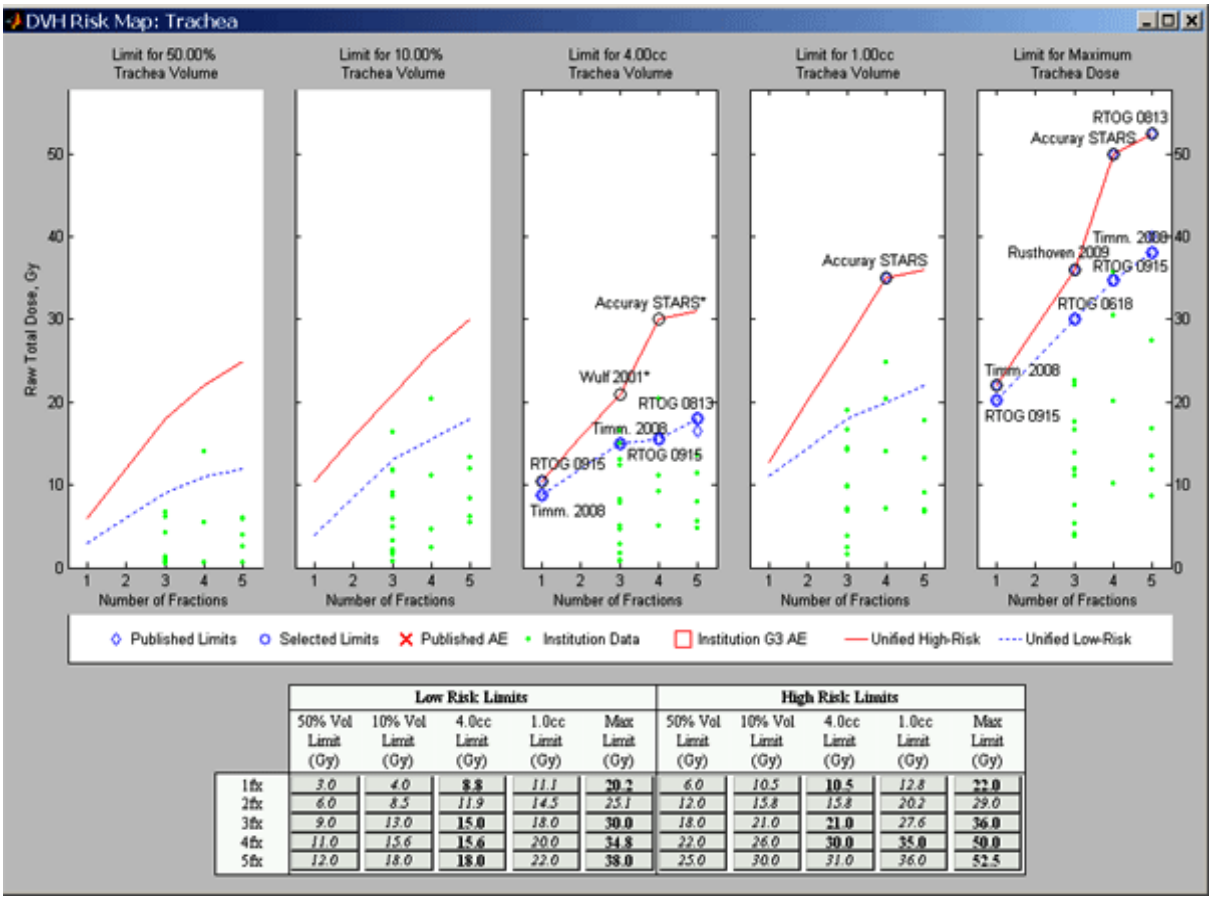
20% in addition to ≥ 5 mm from nadir. Toxicities were graded as per the CTCAE V3 definitions (12) noted in Table 2.

Table 2. Primary Toxicity Endpoints

Critical Structure	Endpoint (≥ G3)
Aorta and Major Vessels	Aneurysm
Bronchi	Stenosis/fistula
Esophagus	Stenosis/fistula
Heart	Pericarditis
Trachea	Stenosis/fistula

RESULTS

No CTCAE Grade 3 or higher adverse events were encountered in this study. The summary of treatment characteristics in Table 1 shows the profound effect of dose tolerance limits on the achievable prescription dose. Although a common goal for SBRT lung treatments is a BED of 100 Gy_{10}, this was only able to be achieved for about two thirds of the cases because of tumor



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1fx	*3.0*	*4.0*	**8.8**	*11.1*	**20.2**	*6.0*	*10.5*	**10.5**	*12.8*	**22.0**
2fx	*6.0*	*8.5*	*11.9*	*14.5*	*25.1*	*12.0*	*15.8*	*15.8*	*20.2*	*29.0*
3fx	*9.0*	*13.0*	**15.0**	*18.0*	**30.0**	*18.0*	*21.0*	**21.0**	*27.6*	**36.0**
4fx	*11.0*	*15.6*	**15.6**	*20.0*	**34.8**	*22.0*	*26.0*	**30.0**	**35.0**	**50.0**
5fx	*12.0*	*18.0*	**18.0**	*22.0*	**38.0**	*25.0*	*30.0*	*31.0*	*36.0*	**52.5**

Figure 7. DVH Risk Map for tracheal toxicity. (Bolded limits are published data and *italicized* are interpolated/extrapolated.)

proximity to critical structures. Since no Grade 3 or higher toxicity was encountered in any of the cases it is likely that higher doses are possible in some areas of the mediastinal region, but this cannot be known for certain until multi-institutional dose escalation studies have completed, so extreme caution is advised until then. This uncertainty in the risk/benefit ratio underscores the importance of ongoing trials like the RTOG 0813 (5) and Accuray STARS (10) protocols, which do allow SBRT within 2 cm of the proximal bronchial tree.

Loss of local control was only observed in two cases. One is still under observation with radiation induced changes versus local progression not determined. Though the crude local tumor control rate was 92%, five of the 15 primary non small cell lung cancer patients developed distant metastasis (33%), and six of the 9 metastatic lung patients developed distant metastasis (67%). The median survival was 26.8 months for the primary lung cases, 9.6 months for the metastatic cases, and 17.2 months over all patients treated.

DISCUSSION

In light of the excessive toxicity reported with SBRT doses of 60-66 Gy in three fractions for central/mediastinal tumors (3) we began mediastinal lung SBRT very cautiously, with some patients receiving a 2 Gy_{10} equivalent dose as low as a conventional 45 Gy. Significantly lower

local recurrence rate with a BED of at least 100 Gy_{10} compared with BED of less than 100 Gy_{10} (8.4% versus 42.9%) has been reported by Onishi et al. (7). It was not feasible for us to prescribe such doses in all patients because of the anatomical location and risk of toxicity. Unger et al. have also used lower BED to avoid complications (13). In Unger's study of 20 patients who underwent CyberKnife treatment for hilar tumors, 30-40 Gy (48-72 Gy_{10}) was prescribed in 5 fractions and the maximum point dose to critical structures was used as guide for limiting toxicities. He reported Grade 3 radiation pneumonitis in 1 out of 17 evaluable patients and 1 patient died due to a bronchial fistula. The low rate of toxicity that we have experienced so far may in part be due to the unparalleled image-guided tracking accuracy of the CyberKnife, our conservative treatment planning techniques, and diligent respect of the dose tolerance limits assisted by the DVH Evaluator.

CONCLUSION

The excellent local control rates reported in the literature are leading to rapidly increasing utilization of SBRT in the treatment of early stage lung tumors and for lung metastasis, but dose tolerance limits for most critical structures throughout the body for SBRT are still uncertain. In our study the minimal toxicity experienced with good local tumor control rate is encouraging. The long term impact of hypofractionated dose delivery to a small volume of normal tissues is still not well understood, and more clinical studies with longer follow up are needed to better define the variables associated with risks of late toxicities. In the meantime, we hope that the data provided on the dose tolerance of dose limiting mediastinal structures will assist the clinicians in their practice and research, and we have found the DVH Evaluator to be a convenient and comprehensive tool in applying the still continually evolving SBRT dose tolerance limits for clinical application.

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