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Research Article

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Abbreviations: 3D Conformal Radiotherapy, (3DCRT); Computer tomography, (CT); Cross Cancer Institute, (CCI); DICOM RT; Dose, (D); Dose-volume histograms, (DVH); Gross tumor volume, (GTV); Gy, (Gray); Helical tomotherapy, (HT); Intensity Modulate Radiotherapy, (IMRT); London Regional Cancer Program, (LRCP); Megavoltage CT, (MVCT); Non-small cell lung cancer, (NSCLC); Ontario, (ON); Planning target volume, (PTV); Volume, (V)

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Summary

Helical tomotherapy (HT) is a novel technique to deliver intensity modulated radiation therapy guided by 3D megavoltage CT imaging. The purpose of our study is to assess the dosimetric parameters related to HT and 3DCRT in advanced non-small cell lung cancer (NSCLC). Eleven patients from the London Regional Cancer Centre and the Cross Cancer Institute with NSCLC underwent individualized treatment planning on both HT and 3DCRT. Corresponding HT and 3DCRT plans for each patient were analyzed using dose-volume histograms for GTV, PTV (median dose 60Gy/30 fractions), and critical structures (lung V5-30, esophageal V50-60, and spinal cord D1). Observed differences in tumor and normal tissue dosimetry were assessed for statistical significance using paired t-tests. A statistically significant improvement on GTV homogeneity but not PTV homogeneity was found in relation with HT. 3DCRT was associated with improved V_5 (14%, p = 0.02), V_{10} (9%, p = 0.04) and V_{15} (6%, p = 0.04). However, there was no difference in V_{20} (2%, p = NS); while HT demonstrated superior V_{30} (5%, p = 0.002). HT achieved excellent tumor coverage relative to 3DCRT in the setting of routinely clinically planned radiation therapy with improvements in the V30 lung parameter. This was at the expense of a modest increase in V_5-V_{15} total lung dose.

I. Introduction

Lung cancer is the second most common malignancy and accounts for 29% of cancer deaths in Canada (Canadian Cancer Society, 2007). Despite aggressive multi-modality treatment of locally-advanced non-small cell lung cancer (NSCLC), 5 year overall survival still remains low at 15-20%. Advancements in tumor imaging, 4-dimensional computed tomography (CT), respiratory gated therapy, image guided therapy, and intensity-modulated radiation therapy delivery are currently being utilized to improve the therapeutic ratio between tumor control and early and late critical structure effects.

Helical tomotherapy (HT) is a novel technique that combines intensity-modulated radiation therapy (with a binary multileaf collimator) with a helical CT (Mackie et al, 1993, 1999). A megavoltage linear accelerator is mounted on a ring gantry, and dose is delivered via a continuous helical beam as the patient progresses through the ring. HT has the ability to produce daily megavoltage CT (MVCT) images, enabling image-guided adjustment of

interfraction setup errors (Ruchala et al, 1999; Ruchala et al, 2000; Welsh 2004) and dose delivery verification (Kapatoes, 2001).

HT has been studied in the context of both traditional (Mehta 2001; Scrimger et al, 2003; Kron et al, 2004) and stereotactic body (Fuss et al, 2006, Hodge et al, 2006) NSCLC treatment. Preliminary investigations of tumor motion effects (Kanagaki et al, 2007), adaptive therapy (Ramsay et al, 2006) and assessment of tumor response by serial MVCT (Kupelian et al, 2005, Seibert et al, 2007) have been reported in the literature. In evaluating stage III locally-advanced NSCLC, mean normalized dose to total lung and the V_{20} were decreased by 30% and 22% respectively using HT when compared to 3DCRT plans (Scrimger et al, 2003). HT also spared both the spinal cord and esophagus. In the comparison of HT to IMRT plans in locally-advanced lung cases including microscopic elective nodal coverage excellent dose homogeneity was found with HT, though this was attained at the expense of higher mean lung dose, esophageal dose, and spinal cord dose (Kron et al, 2004). However, once the elective nodal volume was excluded, the mean lung dose was significantly improved from an average of 28 to 16Gy.

HT has been implemented clinically at each of our institutions since 2003, and prospective evaluation has demonstrated that HT can generate dosimetrically superior equivalent radiotherapy treatment plans compared to 3-dimensional conformal radiotherapy (3DCRT), and that such plans can be delivered safely (Bauman et al, 2007). Concerns regarding low doses of radiotherapy to large volumes of lung tissue have been described in the medical literature (Yorke et al, 2002). With the increasing adoption of arc-based tomotherapy with the potential for delivery of this low dose lung radiation, a dosimetric analysis of this phenomenon is appropriate. Therefore, the objective of our study was to compare HT and 3DCRT NSCLC plans dosimetrically in terms of target and normal tissue parameters in a series of clinically treated patients.

II. Materials and Methods

A. Patients and target design

Eleven patients with NSCLC were included in this study (**Table 1**). Nine patients were treated at the London Regional Cancer Program (LRCP) in London, Ontario, and 2 patients were treated at the Cross Cancer Institute (CCI) in Edmonton, Alberta. All patients had 3-dimensional, multislice CT simulation with 3 mm slice thickness. The gross tumor volume (GTV) was contoured by a thoracic radiation oncologist based on diagnostic CT and pathological information. Positron Emission Tomography was not employed in this treatment cohort. A margin of 1.0 to 2.0 cm was applied around the GTV to define the planning target volume (PTV). Full elective nodal irradiation was not utilized in this study. Lung, esophagus, and spinal cord were contoured for all patients, and these structures were used as avoidance volumes of interest. The total lung was defined as the bilateral external lung contour excluding GTV. The external surface of the esophagus was either contoured from the thoracic inlet to the gastroesophageal junction or for the length of the treatment field depending on institutional/radiation oncologist practice. The external surface of the spinal cord was contoured from the lung apex to the level of L1.

Table 1. Patient demographics.

Variable		
Age		Median 70 years, Range 54-85 years
Gender	Male	n=3 (27%)
	Female	n=8 (73%)
Staging	$T_1N_3M_0$	n=1 (9%)
	$T_2N_0M_0$	n=1 (9%)
	$T_3N_2M_0$	n=4 (36%)
	$T_4N_2M_0$	n=3 (27%)
	$T_4N_3M_0$	n=1 (9%)
	$pT_2N_3M_0$	n=1 (9%)
Tumor Location	Sub aortic fossa	n=1 (9%)
	Lingula	n=1 (9%)
	Left Lower Lobe	n=2 (18%)
	Left Upper Lobe	n=1 (9%)
	Right Middle Lobe	n=1 (9%)
	Right Lower Lobe	n=1 (9%)
	Right Upper Lobe	n=4 (36%)

B. Radiotherapy prescription

A minimum dose of 50 Gy to the PTV was required for entry into the study cohort. The treating radiation oncologist approved the final prescription dose to the PTV and reviewed all DVH information prior to treatment. The median prescription dose was 60Gy in 30 fractions and varied (1 patient at 51.5Gy, 1 patient at 55Gy, and 9 of 11 patients at 60Gy) depending upon the particular clinical scenario. The HT and 3DCRT plans were prescribed to the same total dose, and to the same prescription point. All patients were treated at a standard fractionation of 2 Gy per day. DVH optimization was primarily based on achieving acceptable homogeneity of target dose (GTV and PTV), the reduction of the V_{20Gy} bilateral lung parameter, and clinically acceptable maximum spinal cord dosage (see Helical Tomotherapy and Conventional 3CDRT planning below).

C. Helical tomotherapy planning

CT datasets and all contoured volumes were transferred to the tomotherapy planning workstation (Tomotherapy Inc. Madison, WI, USA) using the DICOM RT protocol. A uniform slice thickness and separation of 3 mm was used after 256x256 voxel CT dataset resampling. The planning system used an inverse planning process based on least-squares minimization of an objective function guided by precedence, importance and penalty factors. The LRCP and the CCI used similar inverse treatment planning parameters, and these have previously been published in the literature (8). The initial lung class solution prioritized GTV coverage and avoidance of contralateral lung, ipsilateral lung and spinal cord. Maximum allowable GTV/PTV target heterogeneity was from -5% to +7% of the prescription dose. The volume of total lung treated to ≥ 20 Gy was limited to a maximum of 35%. The maximum dose to spinal cord was limited to 48Gy. HT planning used pitch of 0.286, fan beam width of 5cm, and initial modulation factor of 3. Dose was calculated using a superposition/convolution algorithm on the normal cell grid setting (256x256). The helical dose delivery was emulated in 51 projections per rotation and the dose calculation used a total of 24 different angles for the dose-spread array of the incident 6 MV beam.

D. Conventional 3DCRT planning

Matched conventional treatment plans were created for

each patient using standard multifield 3DCRT treatment principles. All 3DCRT plans were generated on a commercial treatment planning system (Theraplan Plus 3.8 with Dose Calculation Module 2.0, Nucleotron, Kanata, ON). Coplanar multifield (3-5 fields) 3DCRT planning was performed to optimize target homogeneity, while meeting the same normal tissue dosimetric constraints specified for HT. Field shaping with 120-leaf multileaf collimation was utilized to shape the radiation ports.

E. Statistical Methodology

Dose-volume histograms (DVH) were generated for the GTV and PTV, for both HT and 3DCRT. From these results, PTV and GTV homogeneity indices were calculated for each patient as differences between observed doses: D_5-D_{95} and D_1-D_{99} (where "D_x" represents dose (D, in Gy) received by "x" % of the PTV or GTV).

Considering normal tissue dosimetry, DVHs were generated for the total lung, esophagus and spinal cord, for both HT and 3DCRT, for all patients. From these DVHs, the corresponding fractional organ volumes treated to a set of specified relevant dose levels were identified for the total lung (V_5, V_{10}, V_{15}, V_{20}, V_{30}) and for the esophagus (V_{50}, V_{55}, V_{60}), where "V" represents the fractional volume (%) of an organ treated to a dose of "x" (Gy). For the spinal cord, we calculated the dose to 1% of the organ volume (D_1), the dose to 50% of the organ volume (D_{50}) and the maximum dose to the organ, again for all patients, for both HT and 3DCRT.

All generated dosimetric parameters were compared directly between HT and 3DCRT, and any observed differences were assessed for statistical significance using a two-sided, paired Student's t-test. The *a priori* null hypothesis for all comparisons was that there was no difference in any dosimetric parameter between HT and 3DCRT. The alternative hypotheses were that the difference in DVH parameter between HT and 3DCRT was non-zero.

III. Results

A total of 11 patients with NSCLC were analyzed (**Table 1**). The median age was 70 years old with 3 male and 8 female patients. One patient had a Stage IB tumor, 4 patients had Stage IIIA disease and 6 patients had Stage IIIB disease. Mean GTV was 127.9 cc (range 4.1-282.1 cc), and mean PTV was 391.3 cc, (range 76.6-874.7 cc). Mean spinal cord volume (56.24 cc, range 33.0-96.7 cc), mean total lung volume (4034.3cc, range 1673.6-6611.0 cc), and mean esophageal volume (37.6 cc, range 7.56-67.4 cc) were also calculated. Patients were treated to a median dose of 60Gy (range 51.5-60 Gy) in 30 fractions (range 22-30 fractions) prescribed to the 95% (range 90-100%) isodose line. Ultimately, seven patients were treated with HT and 4 patients were treated with 3CDRT at the discretion of the treating radiation oncologist based on dosimetric analysis and treatment unit availability.

The calculated raw 1%, 5%, 95% and 99% point DVH doses to the GTV and PTV for each of HT and 3DCRT are presented in **Table 2**. The calculated differences between these parameters are presented in this same table. Calculated mean differences (D_1-D_{99}) and (D_5-D_{95}) for the GTV and PTV are presented in this same table. Both (D_1-D_{99}) and (D_5-D_{95}) demonstrated statistically significantly improved homogeneity about the GTV when HT is used. There were no statistically significant differences in PTV homogeneity found between HT and 3DCRT.

The resultant normal tissue dosimetry is presented in **Table 3**. 3DCRT was associated with significantly improved normal lung dosimetry in the range of lowest doses: V_5 (14%, p = 0.02), V_{10} (9%, p = 0.04) and V_{15} (6%, p = 0.04). However, there was no observed difference in V_{20} (2%, p = NS), while HT created a better lung sparing effect at a dose of 30 Gy, V_{30} (5%, p = 0.002). Esophageal V_{50} and V_{55} were not significantly different when comparing 3DCRT to HT; however a small (3%) borderline statistically significant difference (p=0.05) in esophageal V_{60} was observed. The maximal spinal cord dose, D_1 showed a benefit towards 3DCRT with a mean difference of 12.7 Gy (p = 0.02). A categorical analysis of target and normal tissue DVH parameters was also performed (**Table 4**) further emphasizing the differences between the two treatment delivery systems.

Table 2. Target DVH parameters paired T-Test comparison.

	3DCRT		HT		3DCRT-HT		Paired T-Test
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Point Target Dose							
GTV D_1 (Gy)	64.1	2.6	63.9	3.5	0.2	4.5	NS
GTV D_5	63.4	2.7	63.3	3.3	0.1	4.4	NS
GTV D_{95}	58.7	2.3	60.8	2.9	-2.1	2.6	p=0.03
GTV D_{99}	57.7	2.4	60.2	2.4	-2.5	2.7	p=0.01
PTV D_1	64.5	1.9	63.7	3.6	0.8	4.1	NS
PTV D_5	63.5	1.7	62.8	3.3	0.7	3.7	NS
PTV D_{95}	56.8	2.8	57.4	3.8	0.6	2.5	NS
PTV D_{99}	54.2	3.6	54.2	5.5	0.0	2.7	NS
Homogeneity							
GTV D_1-D_{99} (Gy)	11.2	17.5	7.9	13.4	3.3	5.0	p=0.05
GTV D_5-D_{95}	4.1	1.6	2.5	1.5	1.6	2.1	p=0.03
PTV D_1-D_{99}	12.5	8.6	13.0	10.9	-0.5	4.9	NS
PTV D_5-D_{95}	6.7	2.3	5.4	3.7	1.3	3.7	NS

3DCRT= Three-dimensional Conformal Radiation Therapy; HT=Helical Tomotherapy; SD=Standard Deviation; D=Dose; NS=Not Significant

Table 3. Normal tissue DVH parameter paired T-Test comparison.

	3DCRT		HT		3DCRT-HT		Paired T-Test
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Spinal Cord							
D_{50} (Gy)	11.0	14.5	13.5	10.8	-2.5	16.3	NS
D_1 (max dose)	29.1	15.6	41.8	7.0	-12.7	14.8	p=0.02
Total Lung Volume							
V_5	0.50	0.13	0.64	0.17	-0.14	0.19	p=0.02
V_{10}	0.37	0.11	0.46	0.19	-0.09	0.14	p=0.04
V_{15}	0.28	0.10	0.34	0.15	-0.06	0.09	p=0.04
V_{20}	0.23	0.10	0.25	0.11	-0.02	0.06	NS
V_{30}	0.19	0.08	0.14	0.06	0.05	0.04	p=0.002
Esophagus							
V_{50}	0.29	0.21	0.32	0.18	-0.03	0.20	NS
V_{55}	0.26	0.20	0.27	0.17	-0.01	0.17	NS
V_{60}	0.13	0.11	0.16	0.15	-0.03	0.15	p=0.05

V=Volume

Table 4. Categorical target/normal tissue comparison.

	3DCRT>HT	3DCRT=HT	3DCRT<HT
Point Target Dose			
GTV D_1 (Gy)	n=8 (72%)		n=3 (27%)
GTV D_5	n=7 (64%)		n=4 (36%)
GTV D_{95}	n=1 (9%)		n=10 (91%)
GTV D_{99}	n=2 (18%)		n=9 (82%)
PTV D_1	n=9 (82%)		n=2 (18%)
PTV D_5	n=9 (82%)	n=1 (9%)	n=1 (9%)
PTV D_{95}	n=4 (36%)		n=7 (64%)
PTV D_{99}	n=5 (45%)		n=6 (55%)
Homogeneity			
GTV D_1-D_{99} (Gy)	n=9 (82%)		n=2 (18%)
GTV D_5-D_{95}	n=9 (82%)		n=2 (18%)
PTV D_1-D_{99}	n=5 (45%)		n=6 (55%)
PTV D_5-D_{95}	n=6 (55%)		n=5 (45%)
Spinal Cord			
D_{50}	n=4 (36%)		n=7 (64%)
D_1	n=2 (18%)		n=9 (82%)
Total Lung Volume			
V_5	n=1 (9%)		n=10 (91%)
V_{10}	n=3 (27%)		n=8 (73%)
V_{15}	n=3 (27%)		n=8 (73%)
V_{20}	n=3 (27%)	n=1 (9%)	n=7 (64%)
V_{30}	n=10 (91%)		n=1 (9%)
Esophagus			
V_{50}	n=4 (40%)	n=1 (10%)	n=5 (50%)
V_{55}	n=6 (60%)	n=1 (10%)	n=3 (30%)
V_{60}	n=4 (40%)	n=1 (10%)	n=5 (50%)

IV. Discussion

This study was designed to assess the dosimetric benefits of HT versus 3DCRT as it applies to the routine clinical planning and treatment of NSCLC. This report describes the initial clinical implementation experience of helical tomotherapy at two Canadian institutions. Helical tomotherapy plans (and their matched 3DCRT backup plans) were optimized to the level required to achieve safe and clinically appropriate radiation treatment. Other studies assessing non-clinical highly optimized dosimetric comparisons of HT with 3DCRT (10) and IMRT (8) have been previously published in the literature. These investigations were not limited by clinical timeframes and potentially reflect levels of higher optimization that may or may not be clinically achievable in routine practice. Consequently, our results are certainly relevant clinically, with each patient in this study actually received treatment according to one of the two treatment plans (HT or 3DCRT) that was generated. Although the treatment delivered to each patient could potentially have been optimized further (for example to enable delivery of a higher dose to the PTV) such optimization was not performed because the plans already met the standard clinical acceptability criteria in place at each institution at the time of treatment and the added benefits of additional optimization was deemed to be minimal.

With respect to tumor coverage, the HT treatment plans were found to have the advantage of more homogeneous GTV coverage and reduction of total lung V_{30}. This can be appreciated immediately by examining the 30 Gy to 60 Gy isodose lines on a typical treatment plan, as such lines begin to approximate the shape of the PTV very well at this dose level. However, with respect to the total lung volume, HT did not improve the dosimetry to the normal lung in the lowest dose range (20 Gy and less). Although in principle, lung dosimetry in this low-dose region could have been improved slightly through optimization, i.e. by increasing the weighting of the imposed normal lung constraints in the inverse treatment planning optimization algorithm. The dominant factor contributing to the comparatively worse lung dosimetry in the low-dose region is the inherent design of tomotherapy itself. Because of the ring gantry design in tomotherapy, the dose from the arc-based radiation creates a “dose-bath” phenomenon of low dose to normal lung tissue.

For lung cancer (as well as for other thoracic malignancies) the tendency of tomotherapy to increase dose in the low-dose region could have significant negative implications in terms of late toxicity, as there is mounting evidence that the amount of normal lung exposure in the low-dose range is predictive of late toxicity than the amount exposed to higher doses (Yorke et al, 2002). In this regard, further studies are required to establish the potential clinical gain of using HT in routine clinical practice. Therefore, each clinical case should be judged individually, in terms of the dosimetric and image-guidance benefits of HT balanced against the increases in V_5-V_{15} lung DVH parameters. Lung tumors near critical structures such as spinal cord, esophagus, liver, or heart probably provide the best clinical scenarios that can potentially take advantage of the image-guidance and conformal avoidance IMRT capabilities of HT. However, these scenarios were not investigated as part of this report. Patients with large treatment volumes or that are receiving exquisite radiosensitizers may not be the ideal tomotherapy candidates due to the risk of generalized radiation pneumonitis. Clinical studies are currently ongoing at our respective institutions to address and catalogue such therapeutic ratio issues more fully.

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