

Performance evaluation of gated volumetric modulated arc therapy

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ABSTRACT

Background: Aim of this study is to evaluate the accuracy of the gated volumetric modulated arc therapy (VMAT/RapidArc) using 2D planar dosimetry, DynaLog files and COMPASS 3D dosimetry system. **Materials and Methods:** Pre-treatment quality assurance of 10 gated VMAT plans was verified using 2D array and COMPASS 3D dosimetry system. Advantage of COMPASS over 2D planar is that it provides the clinical consequence of error in treatment delivery. Measurements were performed for non-gated and different phase gating window level (80%, 50%, 30% & 20%) to know the impact of gating in VMAT dose delivery. **Results:** In 2D planar dosimetry, gamma agreement index (GAI) for all measurements were more than 95%. DynaLog file analysis shows the average deviations between actual and expected positions of monitor units, gantry and multi-leaf collimator. The STDVs MU and gantry position were less than 0.10 MU and 0.33° respectively. Root mean square (RMS) of the deviations of all leaves were less than 0.58 mm. The results from COMPASS show that 3D dose volume parameters for ten patients measured for different phase gating window level were within the tolerance level of $\pm 5\%$. Average 3D gamma of PTV and OAR's for different window level was less than 0.6. **Conclusion:** The results from this study show that gated VMAT delivery provided dose distributions equivalent to non-gated delivery to within clinically acceptable limits and COMPASS along with Matrix^{Evolution} can be effectively used for pretreatment verification of gated VMAT plans.

Keywords: Gated VMAT, COMPASS, RPM, 3D dosimetry.

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INTRODUCTION

Advanced radiotherapy techniques such as intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and tomotherapy produces high conformal dose distribution compared to conventional two dimensional treatment techniques. These treatment techniques target radiation doses precisely to the shape of tumors, reducing toxicity and side-effects. But for tumors in the thorax and abdomen region, respiratory motion is a limiting factor, which will degrade the effectiveness of conformal radiotherapy (1, 2).

Tumors and organs at risk (OAR's) in thorax and abdomen region move with respect to patient breathing cycle, which increases the planning target volume (PTV) margins thereby increasing the normal tissue complications. Various techniques have been proposed to compensate for tumor motion which includes motion encompassing methods, respiratory gating methods, breath-hold methods, forced shallow breathing with abdominal compression and real time tumor tracking (3-6). In the breath-hold method, the patient is asked to hold breath during the imaging and treatment. In the forced shallow breathing treatment method, a physical

plate is placed and fixed over the abdominal region to restrict breathing motion and thereby limits the excursion of targets and OAR's but this may cause great patient discomfort. Real time tracking technique follows the tumor dynamically with the radiation beam by adjusting the gantry head or multi-leaf collimators (MLC). Respiratory gating is commonly used technique, in which radiation is delivered within a particular portion of the patient's breathing cycle⁽³⁾.

RapidArc (Varian Medical Systems, Palo Alto, CA, USA) is a form of a VMAT, which produces highly conformal dose distribution by simultaneously changing MLC position, dose rate and gantry speed during patient treatment. Many studies have shown the technical feasibility and advantage of VMAT, especially in reducing the treatment time compare to fixed field IMRT⁽⁷⁻¹⁰⁾. In treatment machine the VMAT plan is decomposed into two groups of control parameters. The MLC positions as a function of gantry angle are sent to the MLC controller. The gantry angle as a function of cumulative MU (dose) is sent as a segmented treatment table to the clinac control system^(11, 12). In gated VMAT, when patient breathing portion was outside the window level, beam hold command was sent to dose delivery system by gating system, to interrupt electron injection in the accelerating waveguide. In-sequence, dose delivery system temporarily stops gantry and MLC movement. Due to complex delivery of gated VMAT, it is essential to evaluate and verify the accuracy of the system before its clinical use⁽¹⁾.

Nicolini *et al.*⁽¹²⁾ has shown the pre-clinical evaluation of respiratory-gated delivery of VMAT by using 2D planar dosimetry in homogeneous phantom. Traditional QA procedures (point and 2D planar dosimetry) are performed in a phantom and the criteria that can be used depend on limits of the applied technology, it is often difficult to quantify and interpret the results in terms of clinical impact for the patient. Benjamin *et al.*⁽¹³⁾ shows, there is lack of correlation between gamma passing rates from 2D array and dose differences in critical anatomic regions of interest. The results provided by 2D planar dosimetry cannot be

directly used to see the effects of the dose calculation/treatment delivery errors on the tumour dose or dose to the normal tissues inside the patient⁽¹⁴⁾. To address this issue, alternate QA techniques has been developed to verify the 3D dose distribution in a patient computed tomography (CT) scan by measuring fluence at different gantry angle using ion chamber matrix or electronic portal imaging device (EPID). COMPASS (IBA Dosimetry, Germany) (V3.0) is 3D dose verification system which uses Matrix^{Evolution} and able to reconstruct dose in phantom or patient CT. It consists of measurement-based dose reconstruction and model-based dose calculation.

In measurement based dose reconstruction, (i) Detector dose response is predicted from the patient treatment plan parameters. (ii) Measured dose response from the Matrix^{Evolution} is than compared with predicted dose response. (iii)The difference between the predicted and measured response along with correction kernel was used to derive the reconstruction fluence. Finally reconstructed fluence is fed to the dose engine based on collapsed cone convolution/superposition (CCC/S) algorithm for computation of 3D dose within the patient CT scan. The dose calculated from the reconstructed fluence is referred as "indirectly measured" (COMPASS measured). In model based dose calculations, COMPASS system compute dose in patient CT scan using inbuilt beam model. The purpose of the dose computation is to provide an independent cross-verification of treatment planning system (TPS) calculated dose.

In addition, COMPASS has a facility to compare the 3D dose distribution and dose volume histograms (DVH) between measured and TPS calculated. There are limitations due to the reconstruction capabilities of COMPASS, chamber resolution of MatriXX^{Evolution} and algorithm difference⁽²⁰⁾. So COMPASS may slightly underestimate and/or overestimate the actual delivered dose for PTV and OAR's. Despite local inaccuracies in the dose reconstruction, Godart *et al.*⁽¹⁷⁾ have shown that COMPASS system was adequate to perform pretreatment verification of VMAT treatment plans. Few

studies have shown the experimental and clinical validation of COMPASS system for both IMRT and VMAT⁽¹⁴⁻¹⁹⁾. In this study, we have evaluated the performance of gated volumetric modulated arc therapy by using 2D planar dosimetry, DynaLog Files and COMPASS 3D dosimetry system.

MATERIALS AND METHODS

10 Thorax VMAT plans with two arcs were chosen for this study. Selected cases were pooled from advanced stage (III) lung cancer with a dose prescription of 5000cGy in 25 fractions (Phase-I). The patients mean age was 52.4 years, 57.4% was male and 56.2% patient's tumour was seen on right lung. These patients were immobilized using thermoplastic mask in supine position with both the arms lifted above head on a hemi-body vaclock. Normal free-breathing scan of 3mm slice thicknesses were taken on a Biograph 16 Slice PET-CT scanner (Siemens Medical Systems Concord, CA). After CT scan, the DICOM images were transferred to Eclipse treatment planning system (V8.9) (Varian Medical Systems, Palo Alto, CA, USA) for contouring and planning. VMAT plans were optimized in Eclipse TPS (V8.9) using Progressive Resolution Optimizer -II (PRO) and final dose calculations were performed using Analytical Anisotropic Algorithm (AAA) with 2.5 mm grid resolution⁽¹⁹⁾. These ten patients were treated in normal free breathing using 6 MV photon beam from dual energy Clinac-iX (Varian Medical Systems, Palo Alto, USA). The machine was equipped with millennium 120 multi-leaf collimator, on-board imager and maximum dose rate of 600 MU/min. These ten patients CT data and treatment plans were used to appraise the feasibility and the dosimetric accuracy of gated VMAT. As this was primarily a dosimetric study, where patients were actually treated in free breathing VMAT, dosimetric analysis measurement were performed in phantom and gating was realized by means of the Real-time Position Management (RPM) system from Varian.

RPM respiratory gating system consists of a marker block, an infrared (IR) light ring that emits IR light, a charge-coupled detector (CCD) as a tracking camera used to visualize the relative position of the block, and a workstation that displays and records the motion data as a waveform. The markers box will be placed on the patient's anterior abdominal surface, typically midway between the xyphoid process and the umbilicus. The position of placement must be carefully chosen to maximize the amplitude of the marker motion on the patient. The six reflective fiducial markers were tracked using the IR light source and CCD detector. The six reflecting dots allow the reconstruction of the 3D movements induced by the respiration cycle. In this method, motion of the block was considered as a surrogate for respiratory-induced tumor motion.

To produce the respiratory cycle for our experiment, six dot reflecting marker box was placed on a motion phantom (Varian). It has an elliptical wheel rotating according to a cycle period proportional to the variable voltage applied to the motor driving the wheel. The infrared camera mounted in the treatment room and a workstation converts reflective signals from six markers into respiratory cycle. In respiratory gating, radiation is only delivered in a pre-set window called the "gating window" (figure 1). The gating window can set either in amplitude based or phase based in the desired portion of the respiratory cycle. This gating window determines the radiation beam to on only during a pre-specified part of the respiratory cycle. Measurements were performed for non-gated and four different phase based gating window level (PGWL) (80%, 50%, 30% and 20%) of respiratory cycle (figure 1), i.e., number of interruptions were approximately increased from 5 to 20 times per arc and same were compared with Eclipse TPS calculated dose (performed without any gating). The variations of the duty cycle (the four different phases) were performed on the same respiratory cycle by taking different part of the breathing wave.

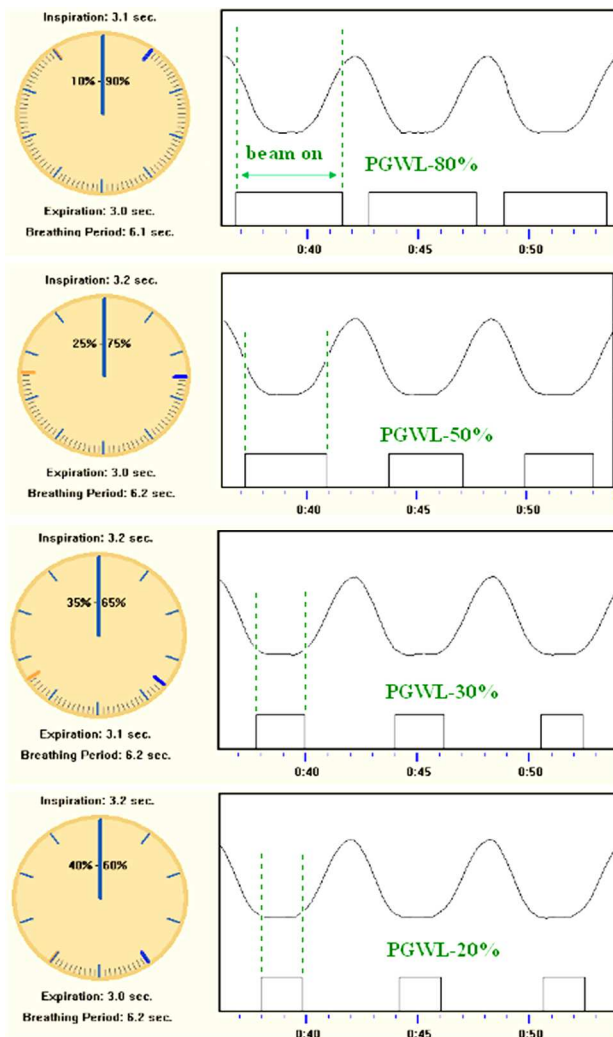


Figure 1. The marker block signal as a function of time from the Varian RPM system. Measurements were performed for four different phases gating window level (PGWL) (80%, 50%, 30% and 20%) of the respiratory cycle, i.e., number of interruptions were approximately increased from 5 to 20 times per arc.

2D Planar dosimetry

For 2D planar dosimetry, multicube phantom with MatriXX^{Evolution} was CT scanned. MatriXX^{Evolution} contains 1020 parallel plane ion chambers (32×32 matrix) with an active area of 24.4 cm ×24.4 cm having 7.62 mm resolution at isocenter 100 cm. To assess the VMAT delivery quality in pre-treatment QA context, verification plans were created on this multicube phantom. In treatment delivery, multicube phantom was placed on couch and infrared reflecting box was periodically moved to provide gating signal for RPM system (figure 2a). To compare

measurements and calculations, planar dose distribution at isocenter level from Eclipse TPS was exported to Omnipro IMRT software (V1.6) (IBA Dosimetry, Germany). To evaluate the agreement between Eclipse TPS calculated and MatriXX^{Evolution} measured, the global gamma analysis were performed with criteria of 3mm distance to agreement (DTA) and 3% dose difference (DD). To check the reproducibility, measurement of one VMAT plan for five different duty cycles were performed for five consecutive days (with the complete setup of phantom and detectors every time). Statistical analyses were performed using the Student's *t-test* (paired, two-tailed) and differences were considered to be significant for *p*-value < 0.05.

VMAT DynaLog files

During the VMAT dose delivery, the linac control systems records log data every 50ms on various parameters. This information was used as a part of overall system QA to evaluate the different parts of VMAT system. Two sets of DynaLog files were created separately by the Clinac and the MLC controller. The Clinac DynaLog file contains both the planned cumulative MU versus gantry angle and the actual cumulative MU delivered versus the actual gantry angle. The MLC DynaLog files contain expected and actual leaf positions^(22, 23). The mean standard deviations in MU and gantry angle and average root mean square (RMS) of the deviations of leaves were compared for the various gated deliveries of ten patients to know the performance of machine under different gated deliveries.

COMPASS 3D dosimetry

For verification of gated delivery, VMAT plans along with patient's CT scan, structure set and 3D dose planes were exported to COMPASS in DICOM RT format. MatriXX^{Evolution} along with 5 cm RW3 buildup plates and gantry angle sensor was placed on linear accelerator using a gantry holder mount (figure 2b) (source to detector distance of 76.2 cm). On treatment machine, dose response was measured by COMPASS using MatriXX^{Evolution}. The infrared reflecting box placed on couch was periodically moved to provide gating signal for RPM system. The response of detector was measured in movie

mode with sampling time of 300ms. COMPASS system predicted dose response using DICOM RT plan parameters (gantry angle, MLC position and MU), detector model and in-built beam model. This predicted dose response at each gantry angle was compared against the corresponding measured dose response and the difference was incorporated in dose calculation (figure 3). The final dose distribution was reconstructed on patient CT using CCC/S

algorithm with same grid size of 2.5 mm. The average doses for PTV, heart, ipsi lateral lung and contralateral lung in ten patients were compared between Eclipse TPS calculated and COMPASS measured. Dose at volume for PTV (D95) and spinal cord maximum dose (D1) was also evaluated. Average 3D global gamma for PTV and OAR's was calculated using criteria of 3mm DTA and 3% DD.

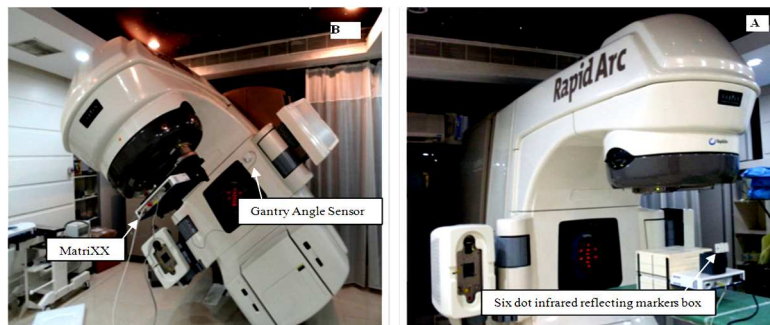


Figure 2. a) 2D planar dosimetry setup for the verification of gated VMAT treatment delivery. Multicube phantom with Matrix^{Evolution} was placed on couch and infrared reflecting box was periodically moved to provide gating signal for RPM system. b) COMPASS 3D dosimetry measurement setup. Matrix^{Evolution} was fixed in gantry mount along with gantry angle sensor and infrared reflecting box placed on couch.

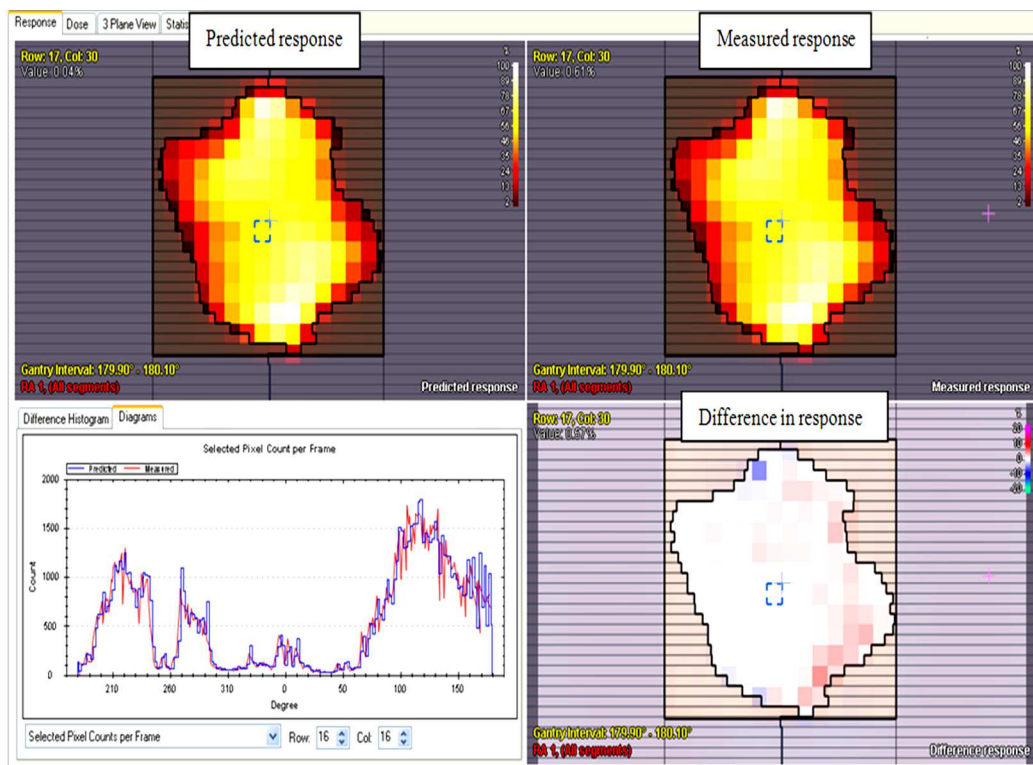


Figure 3. The predicted dose response by COMPASS system was compared against the corresponding measured dose response from Matrix^{Evolution}. The difference in response was incorporated in final dose reconstruction.

RESULTS

2D Planar dosimetry

Table 1 shows the average gamma agreement index (GAI) of 10 patients. GAI is defined as percentage of points passing the gamma evaluation criteria. Gamma analyses between Eclipse TPS calculated and MatriXX^{Evolution} measured, criteria was set as 3mm DTA and 3% DD. For statistical analyses, non-gated was kept as reference. In TPS vs G-VMAT, p value calculated between non-gated and PGWL of 80%, 50%, 30% and 20% were 0.755, 0.133, 0.072 and 0.111 respectively. There was not much statistical significant difference in GAI of four different gated VMAT dose deliveries. Gamma analysis were performed between non-gated measurement and gated measurement. As measurement setup remains unchanged and in order to appreciate the subtle difference in dose delivery between four PGWL, gamma calculating criteria was set stringent by reducing to 1mm DTA and 1% DD. GAI for reproducibility test was more than 99% and found to be statically insignificant (p-value ~1). Results show that all experiments ended with results within acceptability criteria of GAI larger than 95%.

VMAT dynaLog files

For 10 patient's five different deliveries, both the Clinac and MLC DynaLog files were recorded to assess the machine performance. The mean standard deviations between actual and

expected values of the delivered MU and the gantry position were listed in table 1. Average error RMS of all MLC positions for different phase gating was reported in table 1. Figure 4 shows the 10 patients average percentage of leaf position errors for five different phases. The Clinac log file analysis showed good agreement between planned cumulative dose delivered MU versus gantry angle and the actual cumulative dose delivered MU versus gantry angle. For all different phase gating window level, the STDVs MU and gantry position were less than 0.10 MU and 0.33° respectively and showed no visual significant difference. Analysis of the MLC log file indicated good agreement in the actual leaf positions with respect to the planned positions. The RMS of the deviations of all leaves were less than 0.58 mm. There were no systematic drifts in the MU, gantry and MLC positions for different phase gating window level. However there was marginal increase in percentage of MLC error counts for 0.00-0.05mm with respect to decrease in gating window level.

COMPASS 3D dosimetry

In table 2, percentage difference of average dose, percentage difference of D95 and D1 and average 3D gamma between Eclipse TPS calculated and COMPASS measured for PTV's and critical OAR's were listed. Figure 5 shows the dose difference between calculated and measured for PGWL 50% along with DVH comparison. For PTV, irrespective of duty cycle, percentage difference of D95 was less than 3%.

Table 1. Gamma and DynaLog file analysis for different phase gating window level. The values were averaged over the 10 patients.

Parameters	Phase gating window level				
	100% (NG ^e)	80%	50%	30%	20%
GAI ^a - TPS vs Gated VMAT (3mm & 3%)	98.6%± 1.6	98.4%± 1.2	97.4%± 1.8	97.1%± 1.9	97.2%± 2.1
GAI ^a - Non gated vs Gated VMAT (1mm & 1%)	100%± 0.0	99.7%± 0.5	99.4%± 0.7	99.5%± 1.0	98.9% ± 0.9
MLC Average Error RMS ^c (mm)	0.53±0.07	0.52±0.06	0.52±0.06	0.52±0.06	0.51±0.07
STDVs ^d MU	0.07±0.01	0.07±0.01	0.06±0.02	0.07±0.03	0.08±0.01
STDVs ^d Gantry	0.27 ^e ±0.05	0.27 ^e ±0.05	0.27 ^e ±0.04	0.28 ^e ±0.04	0.29 ^e ±0.04

^a gamma agreement index

^b VMAT volumetric modulated arc therapy

^c root mean square of deviations of MLC

^d standard deviations between expected and actual values

^e non gated

For Spinal cord D1 percentage difference was found to be less than 2%. For lungs, percentage difference of average dose was more than 3% which was slightly more than normal clinical range, whereas for all other structures percentage difference was less than 2% which was clinically insignificant. The higher difference in lung was primarily due to difference in algorithm. The dose calculation algorithm in an inhomogeneous medium was completely different in Eclipse TPS and COMPASS 3D dosimetry system. The COMPASS uses CCC/S algorithm, where the dose calculation is based primarily on a point source dose spread array. The Eclipse TPS uses AAA where dose calculation is based on a pencil beam in association with lateral density scaling. In

CCC/S, the dose at a point from a point source of given TERMA (total energy released per unit mass) to the dose at another location in a patient can be calculated by scaling both primary and scatter. Point to point density scaling of this kind is not feasible by the pencil beam kernel method. The point spread kernel based method allows greater flexibility in dealing with 3D inhomogeneous medium than pencil beam kernel. The point kernel-based algorithms (CCC/S) are superior to the pencil beam kernel method (AAA) in handling inhomogeneous region. COMPASS in its current implementation, could measure the delivered dose with sufficient accuracy and could project the 3D dose distribution directly on the patient's CT scan.

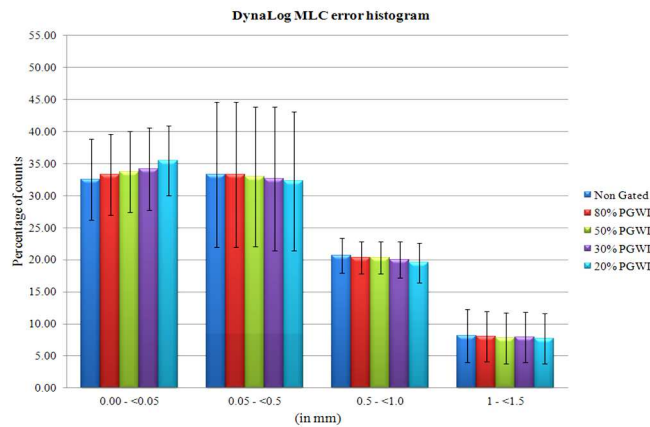


Figure 4. MLC DynaLog file analysis. The bar charts show MLC positional errors for different phases gating window level. The values were averaged over the 10 patients.

Table 2. Dose volume parameters and gamma analysis between Eclipse TPS calculated and COMPASS measured for different phase gating window level. The values were averaged over the 10 patients.

Parameters	Structures	Phase gating window level				
		100%(NG ^a)	80%	50%	30%	20%
% difference in average dose	PTV	2.189 ±1.21	1.953 ±1.44	1.998 ±0.91	1.99 ±0.93	1.753 ±0.7
	Heart	1.739 ±0.72	2.224 ±0.75	2.392 ±1.12	2.319 ±0.96	2.394 ±1.05
	I-Lung ^b	2.945 ±1.26	2.851 ±1.09	2.812 ±1.09	2.905 ±1.09	3.149 ±1.11
	C-Lung ^c	3.835 ±2.07	3.797 ±2.19	3.664 ±2.05	3.841 ±2.18	4.06 ±2.11
% difference in D95	PTV	2.505 ±1.44	1.965 ±0.99	2.332 ±1.44	2.196 ±1.15	2.304 ±1.41
% difference in D1	Spinal cord	1.802 ±0.44	1.300 ±0.38	1.255 ±0.66	1.181 ±0.38	1.196 ±0.5
average 3D gamma (3mm & 3%)	PTV	0.429 ±0.11	0.415 ±0.07	0.460 ±0.09	0.466 ±0.08	0.428 ±0.09
	Spinal cord	0.324 ±0.07	0.331 ±0.10	0.355 ±0.11	0.365 ±0.11	0.372 ±0.13
	Heart	0.300 ±0.12	0.299 ±0.12	0.301 ±0.12	0.297 ±0.12	0.299 ±0.12
	I-Lung	0.399 ±0.06	0.385 ±0.07	0.343 ±0.08	0.367 ±0.06	0.378 ±0.07
	C-Lung	0.235 ±0.08	0.225 ±0.06	0.246 ±0.08	0.224 ±0.06	0.235 ±0.07

^a non gated delivery,

^b ipsilateral lung

^c contralateral lung

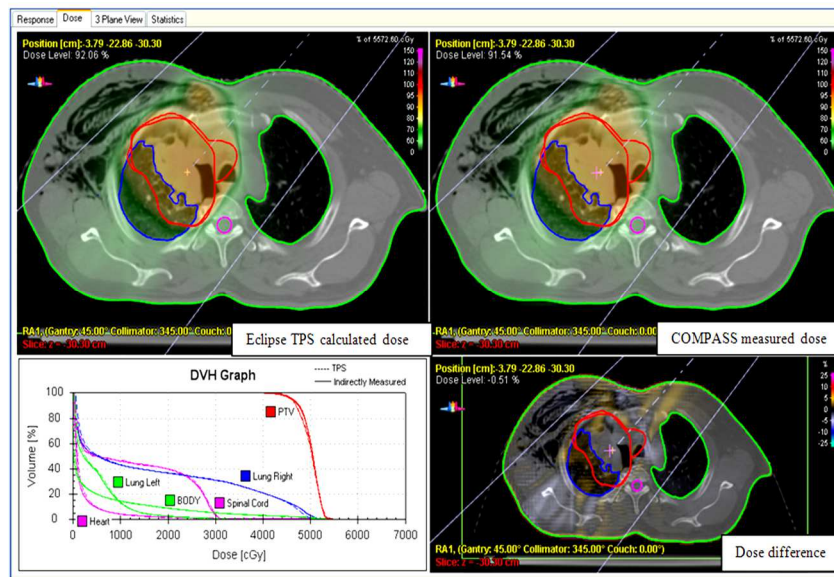


Figure 5. Dose distribution and DVH comparison between Eclipse TPS calculated and COMPASS measured for 50% phase gating window level for a lung patient.

DISCUSSION

Gated VMAT dose measurements were compared with TPS calculated dose distribution (performed without gating) and non-gated dose measurement to appraise the dosimetric impact of the presence of gating in VMAT dose delivery. We have measured four different phase gating window level of 80%, 50%, 30% and 20% (figure 1). The treatment delivery time of gated VMAT was longer than that of non-gated VMAT, for window level 20% the treatment delivery time was increased by factor of 5. But in a clinical treatment the gating window level will be placed around 30%-75% by considering reasonable total treatment time (2). The window level 20% has more than 20 interruptions per arc. The highest number of interruptions means highest potential problems with gantry inertia at release from beam-hold and all possible related mechanical and electronic consequences (12). The results have showed good agreement between TPS calculation and measurement for even very small window level of 20%. Varian RPM system assumes that the motion of external markers correlates with the tumor motion. In this study we did not address the issue of whether respiratory gating signal is appropriate to surrogate internal organ motion. Our primary

intent was to assess machine reliability in delivering gated VMAT. Due to this MatriXX^{Evolution} detector was fixed in a phantom for both 2D planar dosimetry and COMPASS 3D dosimetry while infrared reflecting box was periodically moved to provide gating signal for RPM (figure 2a and 2b). This setup was used to eliminate the uncertainties linked to the accuracy of moving supports and on the synchronization between detector position and gate-open phase.

2D planar dosimetry results show that for all measurements the GAI were larger than clinical acceptability criteria of 95% (12, 24). In spite of reducing gamma calculating criteria to 1mm DTA and 1% DD, there was not much significant difference in GAI between gated and non-gated VMAT dose delivery. Even for 20% phase gating window level, which has highest number of interruptions, the value was $98.9\% \pm 0.9$. For Dynalog files, our values were found to be correlating with Nicolini *et al.* (12) and Teke *et al.* (22) as there are no other internationally acceptable reference values. The extensive analysis of the log files has confirmed the delivery accuracy of gated VMAT treatments. Implementation of patient-specific QA for VMAT was strongly recommended because of the complexity of irregular field shapes, small-field

dosimetry and time-dependent leaf sequences. Adding gating (beam holds) to VMAT increases the complexity further. Therefore it is important to evaluate the feasibility and the dosimetric accuracy of the gated VMAT before its clinical use^(1,5).

The gamma agreement index in table 1 does not provide any clinically relevant information about the results⁽¹³⁾, whereas COMPASS system provides the significance of error in PTV and as well as in OAR's⁽¹⁴⁻¹⁸⁾. The information provided by DynaLog files and traditional 2D planar dosimetry cannot easily be translated onto dose deviations in the tumor and/or at OAR's. However, Qian *et al.*⁽²⁵⁾ have able the reconstruct dose in patient CT scan using trajectory log files from Varian true beam machine, in-house Matlab program and Eclipse TPS for dose verification of respiratory-gated VMAT. On other hand, the advantage of COMPASS 3D dosimetry system over other QA systems was its capability of performing independent 3D dose reconstruction on patient CT scan using beam model, detector measurement and treatment plan. Literatures have validated the accuracy of dose reconstruction method in COMPASS and proved that COMPASS was adequate to perform QA of IMRT/VMAT treatment⁽¹⁴⁻¹⁹⁾. Collapsed cone convolution/superposition algorithm based dose calculation engine in COMPASS system, computes dose distribution in heterogeneous medium (lung) similar to Monte Carlo simulations⁽²⁰⁾. DVH based evaluation will be a good alternative since it allows physicist and physician to accept or reject the treatment plan based on the dose difference in PTV and OAR's (figure 5). The results from table 2 shows that 3D dose parameters for ten patients measured for different phase gating window level were well within the clinically acceptable tolerance level of $\pm 5\%$ ^(24, 26). The average 3D gamma for PTV's and OAR's for ten patients used in this study were less than the recommended value of 0.6 by Visser *et al.*⁽¹⁸⁾. Due to low dose in contralateral lung the percentage difference of average dose was slightly more than ipsilateral lung.

CONCLUSION

The results from this study show that gated VMAT delivery provided dose distributions equivalent to non-gated delivery to within clinically acceptable limits. In 2D planar there is a lack of correlation between performance gamma passing rates and dose errors in anatomic regions-of-interest. Advantage of COMPASS is that it provides the clinical relevance of dose discrepancies between measured and TPS calculated. This study shows that new independent 3D COMPASS QA system can used to ensure the accuracy of gated VMAT treatment delivery.

Conflict of interest: Declared none.

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