REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 24 (2019) 188–199

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Dosimetric impact of statistical uncertainty on Monte Carlo dose calculation algorithm in volumetric modulated arc therapy using Monaco TPS for three different clinical cases

Mohandass Palanisamy[a,b,*], *Khanna David*[a], *Manigandan Durai*[c], *Narendra Bhalla*[b], *Abhishek Puri*[b]

[a] *Department of Physics, School of Engineering and Technology, Karunya Institute of Technology and Sciences, Coimbatore, Tamilnadu, India*

[b] *Department of Radiation Oncology, Fortis Cancer Institute, Fortis Hospital, Mohali, Punjab, India*

[c] *Department of Radiotherapy, Medanta The Medicity Hospital, Gurgaon, Haryana, India*

ARTICLE INFO

Article history:
Received 17 April 2018
Received in revised form
25 September 2018
Accepted 27 January 2019
Available online 18 February 2019

Keywords:
Statistical uncertainty
Monte Carlo dose algorithm
VMAT
Lung
Larynx
Prostate

ABSTRACT

Aim: To study the dosimetric impact of statistical uncertainty (SU) per plan on Monte Carlo (MC) calculation in Monaco™ treatment planning system (TPS) during volumetric modulated arc therapy (VMAT) for three different clinical cases.

Background: During MC calculation SU is an important factor to decide dose calculation accuracy and calculation time. It is necessary to evaluate optimal acceptance of SU for quality plan with reduced calculation time.

Materials and methods: Three different clinical cases as the lung, larynx, and prostate treated using VMAT technique were chosen. Plans were generated with Monaco™ V5.11 TPS with 2% statistical uncertainty. By keeping all other parameters constant, plans were recalculated by varying SU, 0.5%, 1%, 2%, 3%, 4%, and 5%. For plan evaluation, conformity index (CI), homogeneity index (HI), dose coverage to PTV, organ at risk (OAR) dose, normal tissue receiving dose ≥5 Gy and ≥10 Gy, integral dose (NTID), calculation time, gamma pass rate, calculation reproducibility and energy dependency were analyzed.

Results: CI and HI improve as SU increases from 0.5% to 5%. No significant dose difference was observed in dose coverage to PTV, OAR doses, normal tissue receiving dose ≥5 Gy and ≥10 Gy and NTID. Increase of SU showed decrease in calculation time, gamma pass rate and increase in PTV max dose. No dose difference was seen in calculation reproducibility and dependent on energy.

Conclusion: For VMAT plans, SU can be accepted from 1% to 3% per plan with reduced calculation time without compromising plan quality and deliverability by accepting variations in point dose within the target.

* *Corresponding author at*: Department of Physics, School of Engineering and Technology, Karunya Institute of Technology and Sciences, Coimbatore, Tamilnadu, India.
E-mail address: kpmds03@gmail.com (M. Palanisamy).

https://doi.org/10.1016/j.rpor.2019.01.005

1. Background

Volumetric modulated arc therapy (VMAT) is a dynamic arc delivery technique of intensity modulated radiation therapy (IMRT). The advanced modality of VMAT offers dose delivery at a varying gantry speed and dose rate with reduced treatment time as compared to conventional static field IMRT.[1] Many commercially available treatment planning systems (TPS) are available to generate a VMAT plan with different dose calculation algorithms. Dose calculation accuracy in radiotherapy is an important and crucial factor to prevent mistreatment of radiation treatment delivery. Ideally, the dose calculation algorithm should be accurate and able to generate a quality plan with reduced calculation time. Among the commercially available dose calculation algorithms, Monte Carlo (MC) is considered to be potentially more accurate and complex than others.[2–4] Jeraj et al. suggested that because of a large systematic and convergence error, inverse planning system based on pencil beam algorithms alone should be upgraded to MC based dose calculations.[5]

Although Monte Carlo dose calculation algorithms are recognized as the most accurate dose computation algorithms for treatment planning, its inherent statistical uncertainty (SU), determines the accuracy of the dose calculation and calculation time.[6,7] Keall et al.[8] suggested that MC statistical uncertainty decreases inversely with the square root of the computation time. It is a compromise between dose calculation accuracy and acceptable statistical uncertainty. By decreasing the SU, one can increase the dose calculation accuracy. If SU decreases, it results in significant increase of dose calculation time.[9,10] It is a very crucial factor in a busy clinic, where one has to generate several plans, without compromising plan quality and deliverability. To generate clinically acceptable plans with reduced time, the compromise between SU and dose calculation time must be understood and studied properly for various treatment sites.

Keall et al.[8] studied statistical uncertainty on EGS[2]/BEAM[3] and MCVRTP Monte Carlo code and found no statistical uncertainty of 2% or lesser dose in MC calculation does not significantly affect isodose line and dose volume histogram (DVH). Cheong et al. (2004) investigated the effect of statistical uncertainty of photon dose calculation using BEAMnrc and DOXXYZnrc MC simulation systems. He evaluated SU based on DVH, isodose comparison, and root mean-square and reported that acceptable uncertainties were estimated within total 9% error or 1% error over than $D_{max}/2$ voxels or voxels at maximum dose.[11]

Sarkar et al. (2016) used CMS-Monaco™ TPS and investigated the interplay between Monte Carlo variance (MCV) and fluence smoothing factor (FSF) in VMAT for carcinoma of esophagus patients and reported that variation in FSF causes a difference in dosimetric and physical parameters for the treatment plan. The use of MCV between 3 and 5% gives similar results as 1% with shorter calculation time.[12] Antolak reported the uncertainties in dose-response information and other sources of data in the radiotherapy chain. It shed light on our ability to define "how much noise in the dose distributions is acceptable" and to determine the level of dose inaccuracy that may be acceptable.[13]

To the best of our knowledge, no precise data are available for the optimal acceptance level of SU (%) for different treatment sites. Therefore, the purpose of this study was to investigate the impact of the statistical uncertainty on Monaco™ TPS (Version 5.1) in VMAT plans quality and delivery for three different clinical cases.

2. Materials and methods

2.1. Simulation and treatment machine

For this study, three cancer sites which have high heterogeneity, namely the larynx, lung, and prostate were treated with a VMAT technique chosen from the clinical database. A total of 9 patients, 3 from each case were selected for the study. The larynx and lung were immobilized with thermoplastic mold and prostate was immobilized with thermoplastic mold & semi body Vac-Lok cushion. All patients were positioned on a carbon fiber tabletop containing 16 slices PET-CT simulator (Simens® Biograph Truepoint® HD, Siemens AG, Medical solution, Erlagen, Germany) with 70 cm bore size. The patient setup on the CT couch was performed with moving lasers along with three fiducial markers on the patient body for reference. The CT slice thickness of 3 mm was obtained for each clinical case for treatment planning. All VMAT plans were generated using a 6 MV photon beam for Elekta Synergy™ linear accelerator (Elekta Ltd., Crawley, UK) having a 1 cm width multi-leaf collimator (MLC) at the iso-center.

2.2. Contouring and dose prescription

The tumor volume and critical structures were contoured by an experienced radiation oncologist with the support of different image fusions (CT-MRI fusion and CT-PET fusion) as per multidisciplinary protocol of the institute.[14] The doses prescribed to the larynx, lung, and prostate were 70 Gy/33 fractions, 60 Gy/30 fractions, and 79.2 Gy/44 fractions, respectively.

2.3. Target volume delineation and organ at risk

The target delineation, such as gross tumor volume (GTV), clinical target volume (CTV), planned target volume (PTV) and organ at risk volume (OAR) was performed using planning CT images according to the Radiation Therapy Oncology Group (RTOG) guidelines. The OAR volumes were contoured for all three clinical cases, such as bilateral lungs-PTV, Ipsilateral lung, pericardium, esophagus, liver, left parotid, right parotid, spinal cord, oral cavity, bladder, rectum, left femur, right femur, left kidney, right kidney and bowel bag. The body volumes minus all tumor volumes were taken as normal tissue.

2.4. Monaco treatment planning system

Monaco™ V5.1 TPS (IMPAC Medical System, Inc., Maryland Heights, MU, USA) system has a two-stage process of optimizing dose distribution. In the first stage, the ideal fluence distribution of a beam is optimized to meet a user-defined prescription for a single set of beams. In stage two, the

ideal distribution is transmitted into a set of segments where the shapes and weights are optimized based on the same prescription.[15] For the present study, in the first stage, pencil beam algorithm and for the second stage Monte Carlo algorithm was used for dose calculation to generate a VMAT plan. The Monaco™ V5.1 TPS uses SU (%) per plan during the final dose calculation when planners select the Monte Carlo algorithm as the second algorithm. The uncertainty was not the same in all voxels. The low dose voxels in the peripheral regions of the patient had a higher uncertainty of dose than the voxels in the region of the maximum dose (target). The dose uncertainty in the target volume for the final plan was calculated and appeared in the TPS console window after stage-two dose calculation.

The planning system software has an option to choose a different percentage of SU during dose calculations. The statistical uncertainty per plan was the one that the planner was willing to accept for the final dose calculation. However, for a planner, there was an option to accept statistical uncertainty per plan from 0.5%, 1%, 2%, 3%, 4%, and 5% during MC dose calculation.

2.5. *The dosimetric parameter used in treatment planning*

The VMAT plans were generated using partial, full, single and dual arcs. In addition, 3 mm of grid size, 3 mm beamlet width, maximum number of control points 180, minimum segment width of 0.80 cm, medium fluence smoothing and 2% statistical uncertainty per plan were used. By keeping all other parameters constant, plans were recalculated using Monte Carlo dose calculation algorithm only by varying SU, 0.5%, 1%, 2%, 3%, 4%, and 5%. For plan analysis, different dosimetry indices were used as mentioned below.

2.6. *Dosimetric indices used for plan evaluation*

Conformity index (CI): It is defined as the ratio of the volume receiving the prescribed dose ($V_{PTV}^{D100\%}$) and volume of PTV (CI = 1 was an ideal conformity).[16]

$$CI = \frac{V_{PTV}^{D100\%}}{PTV}$$

Homogeneity index (HI): It is defined as the ratio of dose homogeneity in PTV. $D_{2\%}$, $D_{95\%}$, and $D_{50\%}$ are the doses received by 2%, 98% and 50% volume of the PTV dose (HI = 1 was an ideal homogeneity).[17]

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}}$$

Normal tissue integral dose (NTID): It is defined as the product of mean dose of the body (patient volume-PTV) and volume of PTV.[18]

$$NTID[Gy.L] = D[Gy] \times V[L]$$

where D [Gy] is the mean dose delivered to volume V [L] (where L is the liter).

Low dose volume in normal tissues: The contribution of low dose volume in the normal tissue receiving ≥5 Gy and ≥10 Gy were analyzed.

Target dose and critical organ dose: The target (dose to PTV) dose was analyzed as $D_{2\%}$, $D_{95\%}$ and $D_{50\%}$ where Ds were the doses received by 2%, 98%, and 50% of the volume of PTV. Moreover, PTV_{Dmax} was represented to PTV which received a maximum dose. In addition, mean dose (D_{mean}), maximum dose (D_{max}) and dose volume received by different OAR volumes were analyzed for all the three clinical cases.

Dose calculation time ($_t$CT): The dose calculation time was measured from Monaco™ TPS optimization console window which could give dose calculation start and end time for all VMAT plans with different SU value ranging from 0.5% to 5%. For this study, HP Z820 workstations, 32GB RAM, Intel® CPU E5-26700 @ 2.60 GHz (2-Processor), the 64-bit operating system were used. The total calculation time was defined as the time difference between start and finish time of MC dose calculation.

$$_tCT_{mins} = S_{tmins} - E_{tmins}$$

where $_t$CT total calculation time, S_t and E_t start and finish time.

Calculation reproducibility (CR): Calculation reproducibility was evaluated by repeating MC dose calculation five times in the VMAT plan for different SU from 0.5% to 5%. By comparing their plan quality, calculation reproducibility was estimated.

Energy dependence (ED): To estimate energy dependency, the 6 MV photon beam VMAT prostate plan was re-planned with 15 MV photon beam by keeping all planning parameters constant, for different SU values from 0.5% to 5%. The impact of SU% on two different energy plans was analyzed by comparing their quality.

Treatment delivery result: The VMAT plan accuracy was verified using PTW 729 ion-chamber array with OCTAVIUS™ II Phantom (PTW – Freiburg, Germany). The two dimensional (2D) gamma indices were compared at the isocenter between measured dose and TPS planned dose based on the dose to distance agreement (3%, 3 mm and 3%, 2 mm).[19] Similarly, point dose measurement was analyzed using a slab phantom along with 0.125cc Semi-flex chamber (Type 31010) (PTW – Freiburg, Germany).

Isodose comparison: The different isodose lines were compared for SU ranging from 0.5% to 5% in the VMAT plan. For comparison, 6 Gy, 15 Gy, 30 Gy, 45 Gy and 60 Gy isodose lines were used with coronal, sagittal and axial planes.

Statistical analysis: Statistical analysis was performed for all three clinical cases using a One-way ANOVA test to determine the P-value of the analyzed data. The SPSS software (SPSS V.16, IBM, USA) was used for data analysis.

3. Result

The results were analyzed for three different clinical cases by varying SU value of 0.5%, 1%, 2%, 3%, 4% and 5%. A total of 54 VMAT plans were generated for dosimetric comparison. The dosimetric parameter and clinical parameter were evaluated using DVH. Some similarity and differences were observed due to the impact of MC dose calculation uncertainty. The comparison results were analyzed using descriptive and inferential statistics. They were represented with the help of tables, figures, and charts.

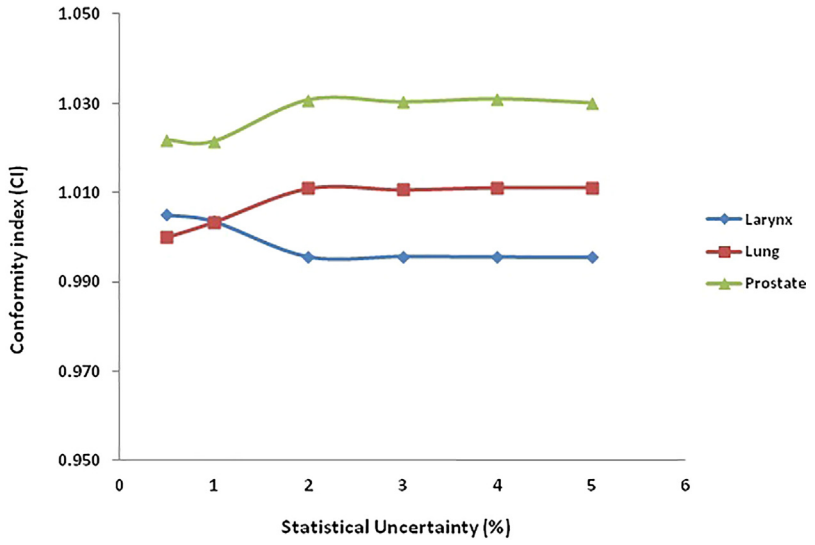

Fig. 1 – Effect of statistical uncertainty on conformity index.

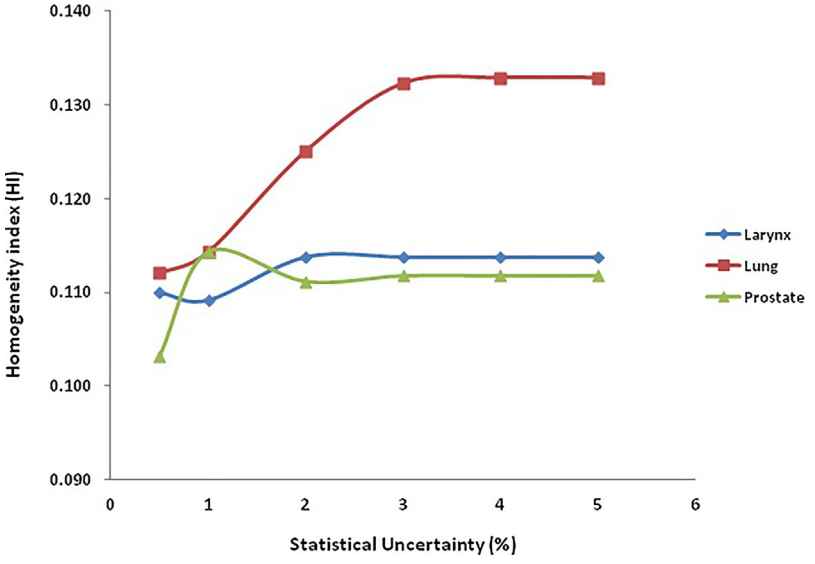

Fig. 2 – Effect of statistical uncertainty on homogeneity index.

In all three clinical cases, HI and CI improved as SU increased from 0.5% to 5%. The dosimetric difference between SU% was observed to be very small and found to be statistically insignificant ($P > 0.05$) as shown in Figs. 1 and 2.

Tables 1–3 depict that the PTV dose coverage was slightly decreased as SU increased from 0.5% to 5% for PTV_{mean}, $D_{98\%}$, $D_{95\%}$, $D_{50\%}$ and the volume received 95% of prescribed dose ($V_{95\%}$). The dose difference was very small and statistically insignificant ($P > 0.05$). However, the maximum dose (D_{max}) to PTV increased as SU increased from 0.5% to 5% with significant dose difference ($P < 0.05$) as shown in Fig. 3.

The normal tissue volume receiving dose ≥5 Gy, ≥10 Gy and NTID was observed to show very small dose difference when SU increased from 0.5% to 5%. The results revealed that the impact of SU% did not make a significant dose difference ($P > 0.05$).

The mean dose and volumetric dose to OAR, such as the left parotid, right parotid, mandible, lung, pericardium, esophagus, liver, bladder, rectum, left femur and right femur showed very small difference. But no clinically and statistically significant dose difference was observed ($P > 0.05$). The maximum dose to the spinal cord and small bowel increased as SU increased from 0.5% to 5% with insignificant dose difference ($P > 0.05$).

The increase of SU leads to the decrease in MC dose calculation time with a significant difference ($P < 0.05$) as shown in Fig. 4.

The gamma index results showed a good pass rate of 98.6%–99.9% for 3%, 3 mm dose to distance agreement for SU from 0.5% to 5% and no significant difference was observed by the influence of SU ($P > 0.05$). The maximum gamma pass rate variation of ≤1% was observed between SU 0.5% and 5%. The results of point dose measurement were observed to have no significant dose difference from 0.5% to 5% and ≤1% dose variation between SU 0.5% and 5% ($P > 0.05$).

Table 1 – Statistical comparison of dosimetric parameters by the influence of statistical uncertainty for larynx VMAT plans (N = 18).

Target and OAR	SU0.5	SU1	SU2	SU3	SU4	SU5	P-value
PTV70							
$D_{98\%}$ (Gy)	6742.46 ± 91.36	6748.00 ± 100.00	6731.90 ± 94.90	6731.90 ± 94.40	6731.90 ± 94.40	6731.900 ± 94.40	1.00
$D_{50\%}$ (Gy)	7269.16 ± 37.06	7265.50 ± 26.10	7250.90 ± 31.80	7250.90 ± 31.80	7250.90 ± 31.80	7250.90 ± 31.80	0.93
$D_{2\%}$ (Gy)	7542.73 ± 77.26	7541.86 ± 72.53	7557.93 ± 70.93	7557.933 ± 70.93	7557.93 ± 70.93	7557.93 ± 70.93	1.00
$V_{95\%}$	99.00 ± 0.93	98.980 ± 1.04	98.86 ± 1.03	98.86 ± 1.03	98.86 ± 1.03	98.86 ± 1.03	1.00
D_{mean} (Gy)	7248.80 ± 40.10	7234.43 ± 14.46	7224.40 ± 26.10	7224.40 ± 26.10	7224.40 ± 26.10	7224.40 ± 26.10	0.81
D_{max}	7751.633 ± 141.86	7796.10 ± 86.20	7935.43 ± 117.53	7935.43 ± 117.53	7935.43 ± 117.53	7935.43 ± 117.53	0.18
HI	0.1100 ± 0.022	0.1092 ± 0.02	0.1138 ± 0.020	0.1138 ± 0.020	0.1138 ± 0.020	0.1138 ± 0.020	1.00
CI	1.0051 ± 0.012	1.0036 ± 0.013	0.9957 ± 0.005	0.9958 ± 0.005	0.9957 ± 0.005	0.9956 ± 0.005	1.00
Spinal cord							
D_{max} (Gy)	4388.63 ± 79.36	4403.63 ± 46.16	4415.90 ± 33.80	4415.90 ± 33.80	4415.90 ± 33.80	4415.90 ± 33.80	0.95
Left parotid							
D_{mean} (Gy)	2402.300 ± 219.80	2402.90 ± 122.00	2408.50 ± 230.70	2408.50 ± 230.70	2408.50 ± 230.70	2408.50 ± 230.70	1.00
D_{50} (Gy)	1773.400 ± 883.90	1771.00 ± 884.50	1783.13 ± 886.16	1783.13 ± 886.16	1783.13 ± 886.16	1783.13 ± 886.16	1.00
Right parotid							
D_{mean} (Gy)	2381.20 ± 253.20	2380.53 ± 252.06	2383.43 ± 257.46	2383.43 ± 257.46	2383.43 ± 257.46	2383.43 ± 257.46	1.00
D_{50} (Gy)	2063.60 ± 563.10	2065.33 ± 569.76	2069.70 ± 579.10	2069.70 ± 579.10	2069.70 ± 579.10	2069.70 ± 579.10	1.00
Mandible							
D_{max} (Gy)	5376.50 ± 1871.10	5400.83 ± 1842.73	5458.46 ± 1878.07	5458.46 ± 1878.07	5458.46 ± 1878.07	5458.46 ± 1878.070	1.00
Normal tissue							
≥5 Gy (cc)	5123.65 ± 321.60	5230.90 ± 217.00	5230.33 ± 221.30	5231.33 ± 220.30	5230.33 ± 221.30	5230.33 ± 221.30	1.00
≥10 Gy (cc)	4301.53 ± 61.13	4302.06 ± 62.37	4301.16 ± 59.67	4303.86 ± 60.03	4303.86 ± 60.03	4301.16 ± 97.20	1.00
NTID (L/Gy)	116.38 ± 5.73	113.52 ± 8.53	116.34 ± 5.54	116.34 ± 5.54	116.34 ± 5.54	116.34 ± 5.54	1.00
Calculation time – CT (min)	8.8 ± 1.9	4.0 ± 2.3	1.6 ± 0.3	1.6 ± 0.3	1.5 ± 0.8	0.7 ± 0.6	0.00
Gamma pass rate (%)							
3%, 3 mm	98.90 ± 2.00	99.73 ± 0.13	98.83 ± 0.63	98.43 ± 0.46	98.90 ± 0.70	98.73 ± 0.53	0.71
3%, 2 mm	98.30 ± 2.40	98.66± 0.86	97.80± 0.50	97.73 ± 0.36	97.76 ± 0.73	97.70 ± 0.20	0.71
Point dose measurement							
% of variation	0.78	0.42	0.20	0.04	0.21	0.21	1.00

PTV, planning target volume; OAR, organ at risk; SU, statistical uncertainty; CI, conformity index; HI, homogeneity index; CT, calculation time, NTID, normal tissue integral dose; cc, volume, mm, distance, D_{max}, max dose; D_{mean}, mean dose; D_{50}, dose received by 50% of volume; $V_{95\%}$ Gy, volume received by 95% prescribed dose.

Table 2 – Statistical comparison of dosimetric parameters by the influence of statistical uncertainty for lung VMAT plans (*N* = 18).

Target and OARS	SU0.5	SU1	SU2	SU3	SU4	SU5	P-value
PTV60							
$D_{98\%}$ (Gy)	5747.36 ± 59.76	5744.16 ± 57.86	5723.76 ± 54.26	5706.26 ± 36.76	5703.16 ± 33.66	5703.16 ± 33.66	0.662
$D_{50\%}$ (Gy)	6175.93 ± 52.23	6173.50 ± 51.20	6167.06 ± 44.96	6165.36 ± 43.26	6163.93 ± 41.83	6163.93 ± 41.83	0.998
$D_{2\%}$ (Gy)	6440.10 ± 83.40	6450.83 ± 86.23	6495.80 ± 87.90	6522.26 ± 114.36	6522.80 ± 114.90	6522.80 ± 114.90	0.765
$V_{95\%}$	98.48 ± 0.69	98.45 ± 0.68	98.23 ± 0.74	98.24 ± 0.31	98.02 ± 0.53	98.02 ± 0.53	0.83
D_{mean} (Gy)	6162.70 ± 58.70	6161.66 ± 57.47	6157.31 ± 26.23	6154.43 ± 54.23	6155.00 ± 49.00	6155.00 ± 49.00	1.00
D_{max}	6728.06 ± 191.33	6723.60 ± 94.20	6902.23 ± 87.77	6948.93 ± 193.83	6992.13 ± 159.33	6992.13 ± 161.47	0.115
CI	1.0001 ± 0.064	1.0035 ± 0.063	1.0110 ± 0.050	1.0107 ± 0.054	1.0112 ± 0.054	1.0112 ± 0.054	1.00
HI	0.1121 ± 0.009	0.1144 ± 0.010	0.1251 ± 0.010	0.1323 ± 0.011	0.1329 ± 0.012	0.1329 ± 0.012	0.069
Spinal cord							
D_{max} (Gy)	3071.40 ± 1152.90	3067.63 ± 1135.47	3125.93 ± 1194.77	3146.23 ± 1174.47	3145.63 ± 1175.00	3145.63 ± 1175.07	1.00
Bilateral lungs-PTV							
D_{mean} (Gy)	1395.10 ± 202.80	1394.56 ± 203.23	1393.76 ± 204.63	1392.93 ± 205.47	1392.76 ± 205.63	1392.76 ± 203.63	1.00
D_{30} (Gy)	1594.20 ± 247.80	1592.53 ± 247.57	1591.10 ± 250.00	1588.90 ± 252.20	1588.50 ± 252.60	1588.50 ± 252.60	1.00
Ipsilateral lung							
D_{mean} (Gy)	843.86 ± 428.43	843.16 ± 428.03	842.23 ± 428.77	842.10 ± 428.90	842.06 ± 428.93	842.06 ± 428.93	1.00
D_{20} (Gy)	1333.10 ± 551.30	1331.73 ± 552.07	1330.53 ± 5524.57	1329.96 ± 553.13	1329.90 ± 553.20	1329.90 ± 553.20	1.00
Pericardium							
D_{10} (Gy)	2721.20 ± 942.50	2723.43 ± 935.07	2724.50 ± 932.60	2715.50 ± 950.60	2715.06 ± 951.47	2715.06 ± 951.47	1.00
D_{33} (Gy)	1275.70 ± 797.90	1276.76 ± 799.43	1277.40 ± 795.60	1274.53 ± 798.47	1274.63 ± 798.37	1274.63 ± 798.37	1.00
D_{67} (Gy)	410.16 ± 415.13	409.96 ± 416.73	409.26 ± 415.93	408.90 ± 416.30	408.86 ± 416.33	408.86 ± 416.33	1.00
Esophagus							
D_{mean} (Gy)	1544.03 ± 926.13	1540.96 ± 924.57	1542.23 ± 921.73	1542.00 ± 922.20	1541.43 ± 923.33	1541.43 ± 923.33	1.00
D_{50} (Gy)	1158.06 ± 686.23	1155.06 ± 682.23	1148.00 ± 684.80	1146.53 ± 686.27	1146.66 ± 686.13	1146.66 ± 686.13	1.00
Liver							
D_{mean} (Gy)	204.70 ± 244.40	205.36 ± 245.13	206.10 ± 245.50	205.93 ± 245.67	205.86 ± 245.73	205.86 ± 245.73	1.00
Normal tissue							
≥5 Gy (cc)	7325.30 ± 2844.80	7326.56 ± 2840.60	7327.33 ± 2842.47	7326.30 ± 2845.30	7326.13 ± 2845.60	7326.13 ± 2845.60	1.00
≥10 Gy (cc)	5117.23 ± 2844.80	5116.20 ± 1808.60	5112.46 ± 1908.16	5110.43 ± 2845.30	5110.00 ± 2845.60	5110.00 ± 2845.60	1.00
NTID (L/Gy)	86.4178 ± 51.50	87.83 ± 48.60	86.24 ± 50.40	86.68 ± 51.25	86.28 ± 50.45	86.28 ± 50.45	1.00
Calculation time – CT (min)	11.8 ± 2.8	3.0 ± 2.1	2.1 ± 1.1	1.9 ± 1.1	1.7 ± 0.8	1.7 ± 1.5	0.00
Gamma pass rate (%)							
3%, 3 mm	99.63 ± 0.43	98.10 ± 1.90	98.53 ± 1.167	98.20 ± 1.80	98.50 ± 1.20	98.66 ± 1.36	0.702
3%, 2 mm	98.20 ± 3.00	96.90 ± 3.50	96.53 ± 3.43	96.06 ± 2.90	95.86 ± 3.33	96.03 ± 2.96	0.921
Point dose measurement (%)							
% of variation	−0.20	−0.49	0.05	−0.12	0.21	0.23	1.00

PTV, planning target volume; OAR, organ at risk; SU, statistical uncertainty; CI, conformity index; HI, homogeneity index; CT, calculation time; NTID, normal tissue integral dose; cc, volume; mm, distance; D_{max}, max dose; D_{mean}, mean dose; D_{10}, D_{33}, D_{50}, D_{67}, dose received by 10%, 33%, 50% and 67% of volume; $V_{95\%}$ Gy, volume received by 95% prescribed dose.

Table 3 – Statistical comparison of dosimetric parameters by the influence of statistical uncertainty for prostate VMAT plans ($N = 18$).

Target and OARS	SU0.5	SU1	SU2	SU3	SU4	SU5	*P*-value
PTV79.2							
$D_{98\%}$ (Gy)	7678.76 ± 121.97	7677.46 ± 120.27	7661.93 ± 104.03	7658.33 ± 111.23	7658.53 ± 110.83	7658.53 ± 110.83	1.00
$D_{50\%}$ (Gy)	8230.60 ± 47.60	8221.10 ± 50.60	8215.30 ± 48.60	8214.26 ± 47.57	8214.26 ± 47.57	8214.26 ± 47.57	0.997
$D_{2\%}$ (Gy)	8528.56 ± 30.47	8541.86 ± 41.27	8575.50 ± 37.20	8577.30 ± 39.00	8577.33 ± 39.03	8577.33 ± 39.03	0.374
V_{95}	99.15 ± 0.88	99.12 ± 0.85	99.07 ± 0.87	99.07 ± 0.87	99.07 ± 0.87	99.07 ± 0.870	1.00
D_{mean} (Gy)	8201.22 ± 41.18	8196.23 ± 41.03	8192.93 ± 39.98	8193.13 ± 39.76	8193.13 ± 39.76	8193.13 ± 39.76	0.998
D_{max}	8784.83± 82.43	8846.80 ± 75.10	9028.50 ± 168.60	9016.66 ± 117.93	9016.60 ± 117.80	9016.60 ± 117.80	0.003
HI	0.1032 ± 0.017	0.1144 ± 0.016	0.1112 ± 0.016	0.1118 ± 0.017	0.1118 ± 0.017	0.1118 ± 0.017	0.961
CI	1.0217 ± 0.010	1.0215 ± 0.037	1.0308 ± 0.045	1.0303 ± 0.044	1.0310 ± 0.045	1.0301 ± 0.016	0.998
Bladder							
D_{mean} (Gy)	5262.16 ± 824.83	5261.26 ± 827.60	5260.36 ± 821.03	5259.73 ± 819.76	5259.73 ± 819.76	5259.73 ± 819.76	1.00
D_{50} (Gy)	5279.60 ± 1120.00	5275.33 ± 1115.70	5272.90 ± 1100.50	5271.20 ± 1097.10	5271.20 ± 1097.10	5271.20 ± 1097.10	1.00
D_{35} (Gy)	6555.23 ± 1052.93	6553.16 ± 1061.17	6561.20 ± 1060.80	6561.13 ± 1060.73	6561.13 ± 1060.73	6560.13 ± 1059.73	1.00
D_{25} (Gy)	7389.23 ± 755.23	7386.36 ± 765.06	7385.73 ± 762.63	7387.06 ± 763.96	7387.06 ± 763.96	7387.06 ± 763.96	1.00
D_{15} (Gy)	7962.36 ± 292.67	7962.13 ± 303.03	7959.46 ± 297.26	7960.56 ± 298.36	7960.56 ± 298.36	7960.56 ± 298.36	1.00
Rectum							
D_{mean} (Gy)	4883.96 ± 224.53	4881.10 ± 227.80	4887.03 ± 22.46	4887.80 ± 223.80	4887.63 ± 223.96	4887.73 ± 223.86	1.00
D_{50} (Gy)	4923.85 ± 164.85	4917.83 ± 169.06	4926.13 ± 166.06	4927.66 ± 169.13	4927.66 ± 169.13	4927.66 ± 169.13	0.982
D_{35} (Gy)	6167.03 ± 72.33	6163.46 ± 55.93	6173.33 ± 72.73	6173.76 ± 73.16	6173.766 ± 73.16	6173.76 ± 73.16	1.00
D_{25} (Gy)	6941.40 ± 85.20	6941.06 ± 84.33	6952.66 ± 93.93	6953.13 ± 93.46	6953.13 ± 96.46	6953.13 ± 93.46	1.00
D_{15} (Gy)	7619.96 ± 84.33	7613.76 ± 91.53	7611.60 ± 100.00	7611.86 ± 99.73	7611.86 ± 99.73	7611.86 ± 99.73	1.00
Bowel bag							
D_{max}	5086.10 ± 2919.80	5069.36 ± 2920.53	5145.33 ± 3003.57	5193.90 ± 3100.70	5193.90 ± 3100.70	5193.90 ± 3100.70	1.00
Rt femur							
D_{mean} (Gy)	2615.43 ± 618.23	2614.26 ± 617.06	2613.16 ± 617.36	2613.86 ± 618.06	2613.86 ± 618.06	2613.86 ± 618.06	1.00
Lt femur							
D_{mean} (Gy)	2760.53 ± 226.63	2759.43 ± 228.73	2758.36 ± 227.67	2758.16 ± 227.46	2758.16 ± 227.46	2758.16 ± 227.46	1.00
Normal tissue							
≥5 Gy (cc)	9480.83 ± 951.63	9486.06 ± 961.07	9489.53 ± 956.23	9488.46 ± 958.37	9488.46 ± 958.37	9488.47 ± 958.37	1.00
≥10 Gy (cc)	8041.26 ± 888.13	8039.20 ± 887.80	8036.00 ± 886.50	8035.56 ± 886.93	8035.56 ± 886.93	8035.56 ± 888.93	1.00
NTID (L/Gy)	192.14 ± 18.33	195.67 ± 15.29	195.87 ± 15.08	195.93 ± 15.26	195.93 ± 15.27	195.93 ± 15.26	1.00
Calculation time – CT (min)	11.8 ± 2.9	4.4 ± 1.2	2.4 ± 1.1	2.3 ± 1.1	2.2 ± 1.0	2.1 ± 0.9	0.00
Gamma pass rate (%)							
3%, 3 mm	99.90 ± 0.20	99.70 ± 0.30	98.96 ± 0.56	99.40 ± 0.60	99.30 ± 0.07	99.30 ± 0.50	0.244
3%, 2 mm	99.80 ± 0.20	99.43 ± 0.56	98.30 ± 0.70	98.46 ± 0.06	98.26 ± 0.46	98.36 ± 0.26	0.001
Point dose measurement							
% of variation	−0.01	0.06	0.32	−0.14	−0.16	−0.22	1.00

PTV, planning target volume; OAR, organ at risk; SU, statistical uncertainty; CI, conformity index; HI, homogeneity index; CT, calculation time; NTID, normal tissue integral dose; cc, volume; mm, distance; D_{max}, max dose; D_{mean}, mean dose; D_{10}, D_{33}, D_{50}, D_{67}, dose received by 15%, 25%, 35%, 50% and 65% of volume; $V_{95\%}$ Gy, volume received by 95% prescribed dose.

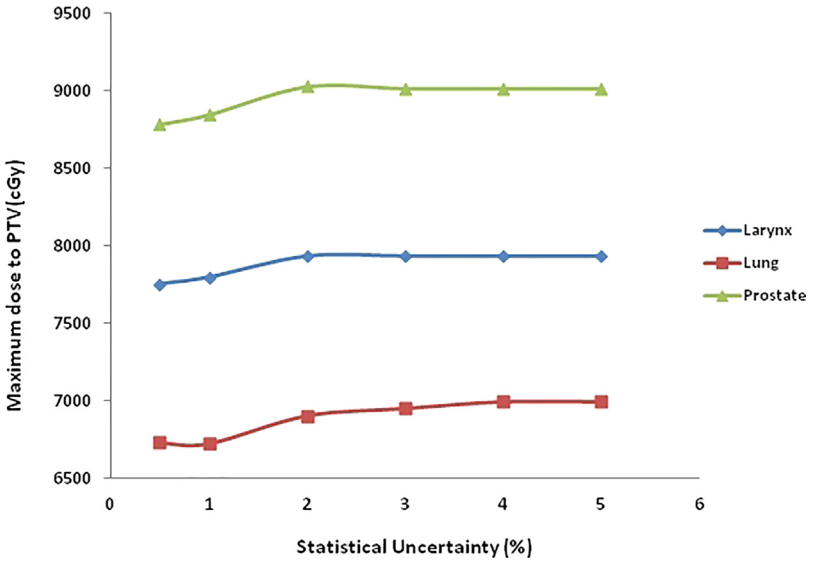

Fig. 3 – Effect of statistical uncertainty on maximum dose to PTV.

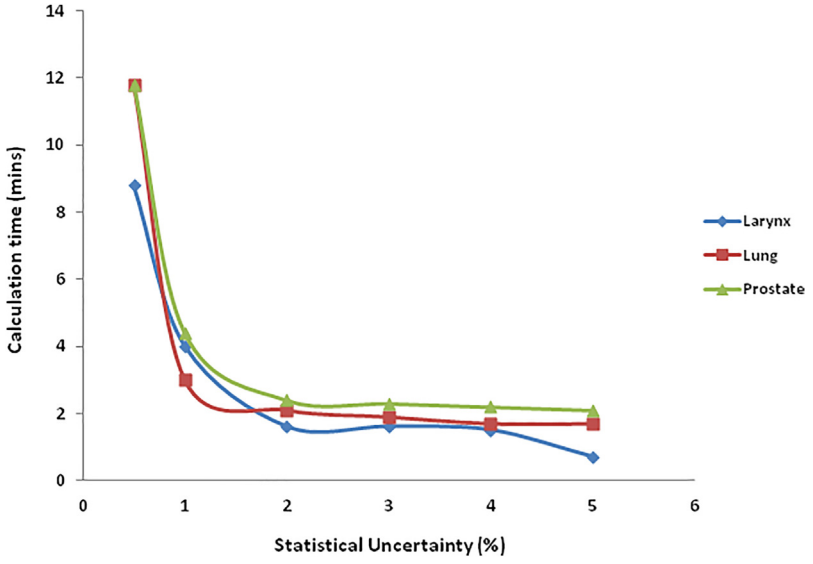

Fig. 4 – Effect of statistical uncertainty on calculation time.

3.1. *Isodose comparison*

Figs. 5–8 depicts that the comparison of different isodose lines and DVH, under the influence of different SU from 0.5% to 5% for the lung VMAT plan. The results between isodose lines were found to be almost similar or identical to each other with less dose difference. The DVH results also showed a very small dose difference between SU 0.5% and 5% and no significant dose differences were observed. Similar results were observed for the larynx and prostate VMAT plan.

3.2. *Calculation reproducibility*

The calculation reproducibility was estimated for the lung VMAT plan after repeating MC dose calculation five times to each SU from 0.5% to 5%. The results showed that no differences were observed in plan quality and deliverability ($P = 1$). Similar results were observed for the larynx and prostate VMAT plan.

3.3. *Energy independency*

The energy dependency was estimated between two different energies of 6 MV and 15 MV photon beam VMAT prostate plans. The qualitative results of CI, HI, dose coverage to PTV, OAR dose, NTID, normal tissue volume receiving dose $\geq$5 Gy and $\geq$10 Gy and gamma pass rate were similar on both plans under the influence of SU from 0.5% to 5%.

4. Discussion

Monte Carlo methods are stochastic techniques that are based on the use of random numbers and probability statistics. All

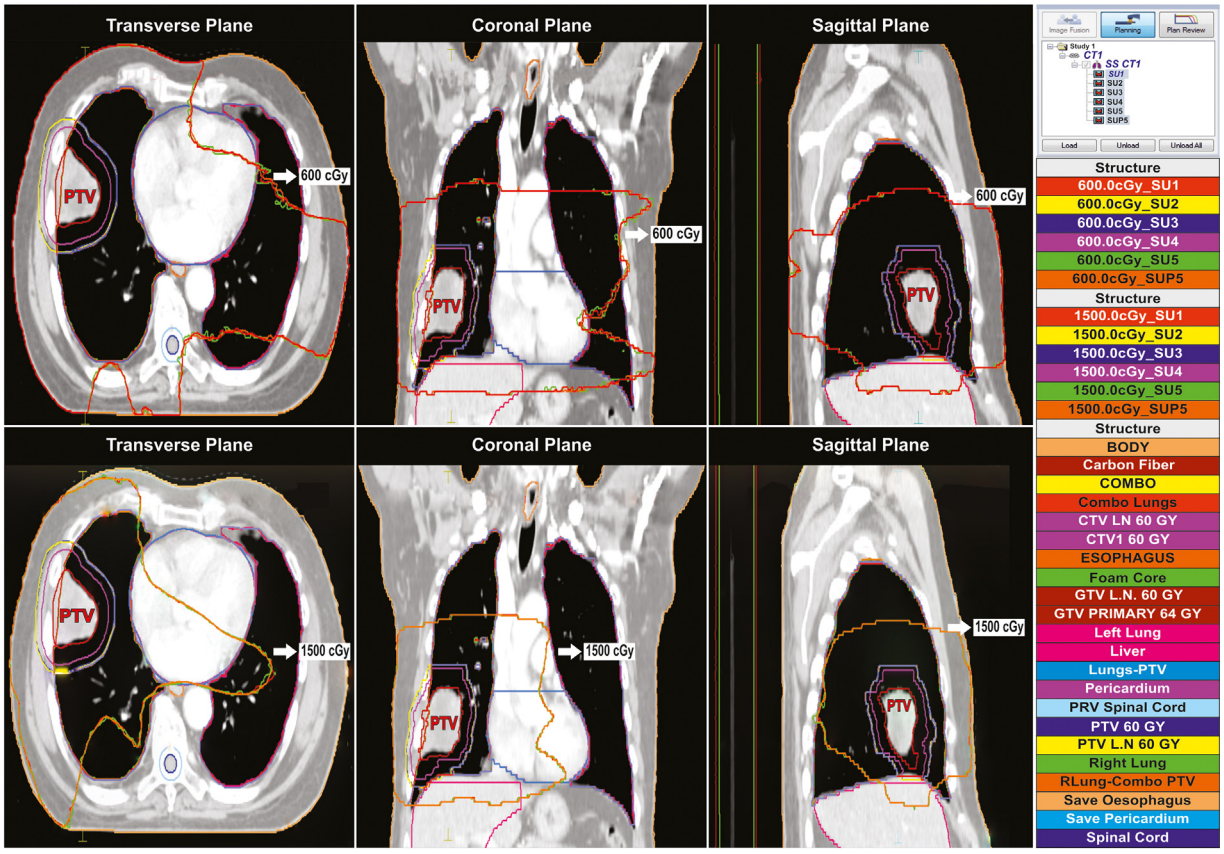

Fig. 5 – Influence of SU 0.5%–5% on 6 Gy and 15 Gy isodose lines.

statistical uncertainties were reported as a function of a total number of simulated histories. The MC dose calculation with no statistical uncertainty is the most desirable in a VMAT plan from the accuracy point of view; however, this would take infinite time to calculate. So the planner should accept a certain range of this calculation uncertainty. The Monte Carlo statistical uncertainty is inversely proportional to the volume of the dose voxels. [13] For example, decreasing the voxel size from 5 to 3 mm, caused the CPU time to increase MC calculation time approximately fivefold. Reducing the SU by a factor of two requires a four-time increase in CPU time. It was very crucial in decreasing/increasing voxel size or SU in both ways. The results of the present study were supported by Chetty et al. (2006) who revealed through their study that determining the acceptable level of statistical precision in MC-computed dose calculation distribution, the tradeoffs between the uncertainties in dose to targets and dose to serial and parallel organs must be considered carefully.[20]

Overall analysis of the present study suggests that there were no site-specific dosimetric variations. The volumetric doses to critical organs did not show any significant variations in different SU values ranging from 0.5% to 5%. Variations were showed in maximum doses within the target, maximum dose to critical organs and calculation time. This effect was significant when the plan was made for the site which had a more serial structure, such as the brain. Similarly, OAR such as the spinal cord, where the biological effect is influenced by the maximal dose, may need to be computed with a much higher precision. However, Radhe Mohan suggests that "dose to a point is not a meaningful quantity when MC techniques are used".[13] Therefore, it is suggested that smaller SU can be used for the cases such as the brain to avoid the variations in the point doses. When SU increased from 0.5% to 5%, the maximum dose to PTV volume increased up to 110% of prescribed dose within the target. However, the dose received by 2 cc volume of PTV did not exceed 110% of prescribed dose. For the present study, it is suggested that SU $\leq$ 2% for serial organs and up to SU3% for target volume should be used.

As reported by Jiang et al. (2000), large statistical uncertainties are expected to 'blur' the DVH curves and the resultant isodose distribution may become unreliable.[21] Mohan and Antonak (2001) reported that beam weighting and dose prescription should be specified in terms of dose to fractional volumes of the tumor volume. The statistical noise should have practically no effect on inverse treatment planning because the intensity along a ray is affected by the average of dose values over a large number of voxels lying along the ray and not by the dose in any one voxel.[13] Since the dose to normal tissues is inconsequential for a given treatment plan, one may consider using larger SU for the plan. It was suggested that large SU can be used for large tumors and OARs such as parallel organs. The effect of statistical uncertainty in the present study showed no significant dose difference on the mean dose to the target and OAR volumes. Therefore, it is suggested that SU can be used up to 5% for parallel organs.

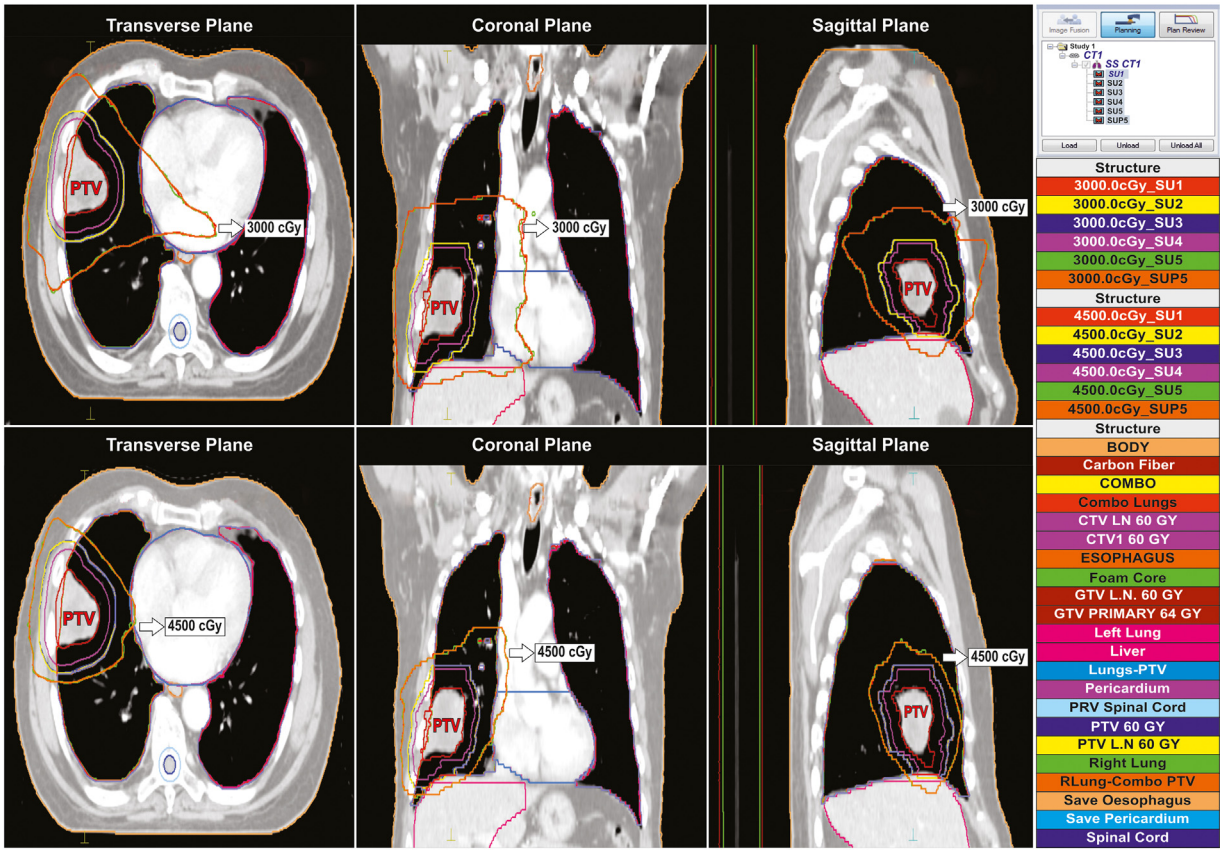

Fig. 6 – Influence of SU 0.5%–5% on 30 Gy and 45 Gy isodose lines.

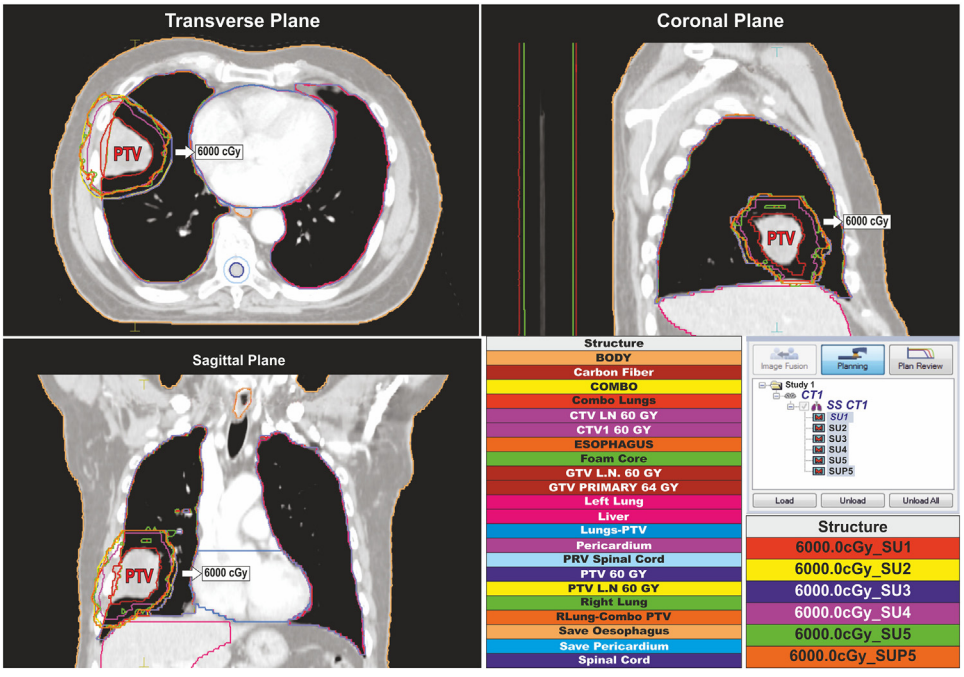

Fig. 7 – Influence of SU from 0.5% to 5% on 60 Gy isodose line.

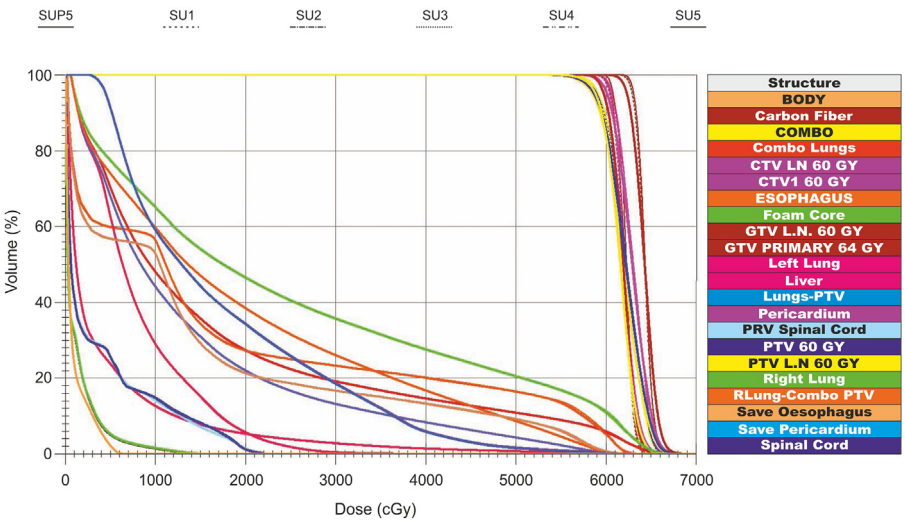

Fig. 8 – Effect of SU 0.5%–5% on lung VMAT dose volume histogram.

Significant variation was observed in calculation time as SU increased. It is suggested that SU optimal range from 1% to 3% can be used without compromising plan quality. Because no significant variations were observed in the gamma pass rate and point dose results, It is suggested that SU from 0.5% to 5% should be used. The QA devices had a limited number of detectors to match computed dose to measured dose. Therefore, it was suggested to use smaller SU values such as ≤2% during dose calculation in TPS for pre-treatment verification. The calculation reproducibility was excellent in MC dose calculation for SU ranging from 0.5% to 5% with similar results. The impact of SU on MC dose calculation assured that it was independent of photon energy. Moreover, the comparison of SU on the low dose and high dose isodose lines of 6 Gy and 60 Gy showed a very minimum difference between SU 0.5% and 5%.

5. Conclusion

The present study assured the optimal acceptable range of statistical uncertainty on Monte Carlo dose calculation during treatment planning in Monaco™ V5.1 TPS. For all the three clinical cases, in VMAT pan, SU can be accepted from 1% to 3% per plan with reduced calculation time without compromising the target coverage, OAR doses and plan delivery only by accepting variation in the point dose and inhomogeneous dose within the target. Moreover, the evaluation of calculation reproducibility and energy dependency substantiated the accuracy of the Monte Carlo dose calculation. The SU% had excellent dose calculation reproducibility in the Monte Carlo algorithm and it was independent of photon energy.

Conflict of interest

None declared.

Financial disclosure

The authors did not receive any kind of grant or financial support from any organization for the present study.

REFERENCES

1. Teoh M, Clark C, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. *Br J Radiol* 2011;**84**(1007):967–96, http://dx.doi.org/10.1259/bjr/22373346.
2. Vanderstraeten B, Reynaert N, Paelinck L, et al. Accuracy of patient dose calculation for lung IMRT: a comparison of Monte Carlo, convolution/superposition, and pencil beam computations. *Med Phys* 2006;**33**(9):3149–58.
3. Zhao Y, Qi G, Yin G, et al. A clinical study of lung cancer dose calculation accuracy with Monte Carlo simulation. *Radiat Oncol* 2014;**9**:287.
4. Jabbari K. Review of fast Monte Carlo codes for dose calculation in radiation therapy treatment planning. *J Med Signals Sensors* 2011;**1**(1):73–86.
5. Jeraj R, Keall P, Siebers J. The effect of dose calculation accuracy on inverse treatment planning. *Phys Med Biol* 2002;**47**(3):391–407.
6. Ma C, Mok E, Kapur A, et al. Clinical implementation of a Monte Carlo treatment planning system. *Med Phys* 1999;**26**(10):2133–43.
7. Kawrakow I. The effect of Monte Carlo statistical uncertainties on the evaluation of dose distributions in radiation treatment planning. *Phys Med Biol* 2004;**49**(8):1549–56.
8. Keall P, Siebers J, Jeraj R, Mohan R. The effect of dose calculation uncertainty on the evaluation of radiotherapy plans. *Med Phys* 2000;**27**(3):478–84, http://dx.doi.org/10.1118/1.598916.
9. Ma C, Li J, Jiang S, et al. Effect of statistical uncertainties on Monte Carlo treatment planning. *Phys Med Biol* 2005;**50**(5):891–907.
10. Ma C, Pawlicki T, Jiang S, et al. Monte Carlo verification of IMRT dose distributions from a commercial treatment

planning optimization system. *Phys Med Biol* 2000;**45**(9):2483–95 [PMID: 11008950].
11. Cheong K-H, Suh T-S, Cho B-C. The effects of the statistical uncertainties in Monte Carlo photon dose calculation for the radiation therapy. *J Korea Assoc Radiat Prot* 2004;**29**(2):105–15.
12. Sarkar B, Manikandan A, Nandy M, Munshi A, Sayan P, Sujatha N. Influence of Monte Carlo variance with fluence smoothing in VMAT treatment planning with Monaco TPS. *Indian J Cancer* 2016;**53**(1):158.
13. Mohan R, Antolak J, Hendee W. Monte Carlo techniques should replace analytical methods for estimating dose distributions in radiotherapy treatment planning. *Med Phys* 2001;**28**(2):123–6.
14. ICRU. *Report 83 prescribing, recording, and reporting photon-beam intensity modulated radiation therapy (IMRT). International Commission on Radiation Units and Measurements*; 2010. Bethesda.
15. *Monaco training guide*. Sweden: Elekta AB, Stockholm: Impac Medical Systems Inc.; 2013.
16. Feuvret L, Noël G, Mazeron J, Bey P. Conformity index: a review. *Int J Radiat Oncol Biol Phys* 2006;**64**(2):333–42, http://dx.doi.org/10.1016/j.ijrobp.2005.09.028.
17. Nithya L, Raj N, Kumar A, Rathinamuthu S, Pandey M. Comparative analysis of volumetric-modulated arc therapy and intensity-modulated radiotherapy for the base of tongue cancer. *J Med Phys* 2014;**39**(2):121, http://dx.doi.org/10.4103/0971-6203.131288.
18. Aoyama H, Westerly D, Mackie T, et al. Integral radiation dose to normal structures with conformal external beam radiation. *Int J Radiat Oncol Biol Phys* 2006;**64**(3):962–7, http://dx.doi.org/10.1016/j.ijrobp.2005.11.005.
19. Hussein M, Adams E, Jordan T, Clark C, Nisbet A. A critical evaluation of the PTW 2D-ARRAY seven29 and OCTAVIUS II phantom for IMRT and VMAT verification. *J Appl Clin Med Phys* 2013;**14**(6):274–92, http://dx.doi.org/10.1120/jacmp.v14i6.4460.
20. Chetty I, Rosu M, Kessler M, et al. Reporting and analyzing statistical uncertainties in Monte Carlo-based treatment planning. *Int J Radiat Oncol Biol Phys* 2006;**65**(4):1249–59.
21. Jiang S, Pawlicki T, Ma C. Removing the effect of statistical uncertainty on dose-volume histograms from Monte Carlo dose calculations. *Phys Med Biol* 2000;**45**(8):2151–61.