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Software simulation of tumour motion dose effects during flattened and unflattened ITV-based VMAT lung SBRT

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ABSTRACT

Purpose: Restricted studies comparing different dose rate parameters are available while ITV-based VMAT lung SBRT planning leads to perform the analysis of the most suitable parameters of the external beams used. The special emphasis was placed on the impact of dose rate on dose distribution variations in target volumes due to interplay effects.
Methods: Four VMAT plans were calculated for 15 lung tumours using 6 MV photon beam quality (flattening filter FF vs. flattening filter free FFF beams) and maximum dose rate of 600 MU/min, 1000 MU/min and 1400 MU/min. Three kinds of motion simulations were performed finally giving 180 plans with perturbed dose distributions.
Results: 6FFF-1400 MUs/min plans were characterized by the shortest beam on time (1.8 ± 0.2 min). Analysing the performed motion simulation results, the mean dose (Dmean) is not a sensitive parameter to related interplay effects. Looking for local maximum and local minimum doses, some discrepancies were found, but their significance was presented for individual patients, not for the whole cohort. The same was observed for other verified dose metrics.
Conclusions: Generally, the evaluation of VMAT robustness between FF and FFF concepts against interplay effect showed a negligible effect of simulated motion influence on tumour coverage among different photon beam quality parameters. Due to the lack of FFF beams, smaller radiotherapy centres are able to perform ITV-based VMAT lung SBRT treatment in a safe way. Radiotherapy department having FFF beams could perform safe, fast and efficient ITV-based VMAT lung SBRT without a concern about significance of interplay effects.

1. Introduction

Technical development in radiotherapy has enabled the delivery of radiation with a high degree of accuracy, giving new opportunities for improving the whole external beam radiation treatment.[1] It is very important especially while performing complicated external beam radiation treatments as in the case of lung cancer. Undoubtedly, respiratory motion (as it can be up to several centimetres) is the dominant factor, which has to be included and verified during lung tumour irradiation.[1–4] Consequently, the ITV-based irradiation and gated or tracked radiation delivery are the most commonly used breathing management strategies utilized to achieve and provide an adequate dose distribution in the tumour tissues[5–8] both during conventional 2-Gy per fraction schemes as well as stereotactic body radiation therapy (SBRT) treatments.[1,8] Numerous literature findings report that from a technical point of view, the best way to achieve sharp dose fall-off outside the target to avoid normal tissue toxicity, is by using dynamic treatment delivery options, especially volumetric arc therapy (VMAT).[9–13] Apart from achieving the desired dose distribution, VMAT dynamic delivery offers the possibility to shorten daily treatment time compared with 3-dimentional conformal (3DCRT) and intensity-modulated radiation therapy (IMRT) treatments.[9,13–16] On the other hand, for SBRT VMAT, there is a concern about the significance of interplay effects among the respiration-induced tumour movement, fluence, gantry and multileaf collimator (MLC) motion which tend to average out over the course of treatment.[17] Studies performed at the

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beginning of this decade pointed out that interplay effects tended to be less prominent with longer delivery times, larger number of beams and larger number of fractions.[3] This would suggest that in clinical practice lower dose rates usage would reduce the interplay effect. Restricted studies comparing different dose rate parameters available while VMAT lung SBRT planning forced the authors to perform the analysis of the most suitable technical parameters of the external beams used. Thus, knowing all features of flattened and unflattened photon beam quality, our goals were to (i) compute 4 treatment plans for each of 15 NSCLC cases, (ii) examine dosimetric accuracy of the prepared plans, (iii) evaluate the differences between the number of monitor units and beam on time among the calculated treatment plans. The special emphasis was placed on the impact of dose rate on the dose distribution variations in target volumes while taking into account the breathing motion and the possible interplay between gantry rotation, MLC and respiration-induced tumour movement.

Such data will give valuable insights into the details of photon beam quality used for VMAT employed for the SBRT lung cancer patient cohort.

2. Materials and methods

2.1. Patient characteristics

15 tumours of 12 patients treated in our institute were retrospectively chosen. The study included patients with NSCLC unsuitable for surgical approach due to age or co-morbidity. One third of the patients were women, the other two thirds were men. The whole group was characterized by the median age of 59 years (range: 34–82 years). Target lesions were distributed as follows: 29% in the upper, 21% in the middle, and 9% in the lower lobes of the right lung; and 29% in the upper and 12% in the lower lobes of the left lung.

2.2. Immobilization, CT scanning and delineation procedure

Patients were positioned and treated in a supine position via vacuum mattress with hands along the body. Planning computed tomography (CT) was acquired with 1 mm slice thickness using Somatom Sensation Open CT scanner (Siemens Medical Solutions, Erlangen, Germany). To define the motion trajectory of the tumour, four-dimensional computed tomography (4DCT) was performed. The volumetric data, which represented bins of one breathing cycle, were used for further analysis, as the gross tumour volume (GTV) was defined by a single experienced clinician on each of the respiratory series.[9,17–20] Then, those contours were reviewed by a senior radiation oncologist.[4,21,22] GTVs approved from each bin were copied to planning CT scans as: GTV0 (from the first 4DCT bin identified the maximum normal inspiration), GTV10, GTV20, GTV30, GTV40, GTV50 (from the medial 4DCT bin recognized maximum normal expiration), GTV60, GTV70, GTV80, GTV90, GTV100.

According to the results published in Neoplasma,[4] the peak to peak motion (PtP) was chosen to characterise the tumour position changes during one breathing cycle. Precisely, PtP was obtained by subtracting the minimum tumour coordinate from the maximum coordinate value.

After adding the target position during each phase of respiratory cycle, the established motion envelope was defined as internal target volume (ITV).[10,12,20,23] The planning target volume was delineated as the structure created by adding 5-mm margin to ITV.[15,23–25] In addition, OARs, such as: lungs, heart, spinal cord, oesophagus and, if relevant, also chest wall, brachial plexus, large blood vessels, ribs, liver or bronchial tree, were contoured.

2.3. Treatment planning

Treatment plans were computed with total doses ranging from 48 to 55 Gy with a dose per fraction varied from 10 to 12.5 Gy. The dose was prescribed individually depending mainly on target location.[9,21,26–28]

Four different VMAT treatment plans (RapidArc v13, Varian Medical Systems, Palo Alto, CA, USA) were calculated for each patient using 6 MV photon beam quality[28,29] and maximum dose rate:

(i) 6FF-600 MU/min,
(ii) 6FFF-600 MU/min,
(iii) 6FFF-1000 MU/min,
(iv) 6FFF-1400 MU/min,

Where FF characterized beams with a flattening filter and FFF described beams generated without the flattening filter.

All plans were computed using the Eclipse Treatment Planning System v. 13.6 (Varian Medical Systems, Palo Alto, CA) on free-breathing CT images with anisotropic analytical algorithm (AAA) used to calculate the dose.[9,21,30,31] The plans were optimized for a Varian TrueBeam (Varian Medical Systems, Palo Alto, CA, USA) equipped with a Millenium 120 mulitileaf collimator (MLC) with spatial resolution of 5 mm at the isocentre.

While starting the planning procedure with RapidArc (RA) two coplanar, partial arcs were proposed. The application of two arcs instead of one was connected with the fact that it is better for an optimizer to work having twice as many control points. If needed, when two arcs were not sufficient to prepare a treatment plan with a sharp dose fall-off, the additional partial arc or arcs were added. The requirement was to limit the arcs rotational length to the ipsilateral lung while avoiding the arm. Such strategy reduced the beams' entrance and their exit through the contralateral lung.[11,14] The collimator angle was set alternately at 30° and 330° in order to reduce the effect of tongue and groove leakage. The collimator angle was set alternately at 30° and 330° in order to reduce the effect of tongue and groove leakage.[25] In every version of the prepared treatment plans, OARs dose constraints were kept as low as possible strictly respecting the dose tolerance limits defined by Grimm et al.[32]

To compare the flattened with unflattened beams, first, the calculation for a flattening filter beam was designed with the dose rate of 600 MU/min. Then, using the same geometry and dose constraints, the three additional plans were optimized for a flattening filter free beam with the dose rates of 600 MU/min, 1000 MU/min and 1400 MU/min. Taking into account plan quality, all the target and OAR objectives were met in all the computed plans.

2.4. Pre-treatment verification of VMAT lung SBRT plans

The ArcCHECK (Sun Nuclear Corporation, Melbourne, USA) measurements were used to perform the gamma analysis with local dose tolerance and distance-to-agreement (DTA) of 2%/3 mm. The score value was evaluated to define the percent value of the measured points for which calculated gamma was correct.

2.5. Software motion simulation

The impact of simulated motion on delivered dose distribution was verified for 60 treatment plans using the MotionSim feature available in 3DVH version 3.3.2 (Sun Nuclear Corporation, Melbourne, USA). This specific module is utilized to generate motion trajectory information based on 4D contours achieved from 4DCT imaging data and using the following information:

(i) patient planning CT and treatment plan data exported from treatment planning system,
(ii) patients' motion trajectory details,
(iii) ArcCHECK verification plan *exported/sent* from treatment planning system,
(iv) delivered dose measured on an ArcCHECK device (Sun Nuclear Corporation, Melbourne, USA) and saved in a special format (acml files).

Precisely, the MotionSim superimposes structure's motion trajectory onto the ArcCHECK delivered dose (machine delivery data files) and reconstructs it in 3DVH software. For every plan, three kinds of motion simulations were done:

(i) 1 Phase (1Ph) – the effect of motion simulated as it would be always delivered starting with the first defined breathing phase (in the case of the performed simulation it was the maximum normal inspiration),
(ii) Random Phases (RanPh) – by perturbing all fractions with random phases,
(iii) Statistical Mean (StatMean) – simulation made with sampling density (meaning the simulation sampling bins) of 10, which according to the manufacturer, was empirically determined as the number of fractions needed to average out the impact of motion for a VMAT case,

Finally giving 180 plans with perturbed dose data.

Quantitatively, the estimation of the potential impact resulting from the interplay between moving tumours and dynamically delivered external beam radiotherapy, was performed using DVH metrics. For GTV, ITV, PTV (delineated on planning CT) and GTV0-100 (contours originally delineated on every 4DCT bins and copied into planning CT), minimum (Dmin), maximum (Dmax) and mean (Dmean) doses were estimated. Additionally, for GTV, ITV and PTV, the D95%, D98% and D99% (while Dx% is the dose at certain x% volume) were evaluated. Precisely, the impact of the motion on the dose distribution was verified calculating the difference between comparison (meaning simulated dose) and reference doses (from original treatment plan). To facilitate comparisons across a variety of fractionation and cumulative dose prescribed, all the dose parameters (Dmin, Dmax, Dmean, D95%, D98%, D99%) were presented as percentage (%) differences.

2.6. Statistical analysis

Statistical analysis was performed using XLSTAT software version 2019.3.2 (Addinsoft. XLSTAT statistical and data analysis solution, Boston, USA) with p-value below 0.05 deemed to be statistically significant. According to the results of the Shapiro Wilk test, the majority of examined samples represented the non-normal distribution. Thus, the Friedman test was used to verify the dependence between them. Based on normality of the samples and positive test for variance compliance, the ANOVA, utilizing multiple comparison, was used to investigate the statistical significances between the plans performed for different photon beam qualities (6FF-600 MU/min vs. 6FFF-600 MU/min vs. 6FFF-1000 MU/min vs. 6FFF-1400 MU/min).[13] Furthermore, to allow the beam rate to be separated from flattened and unflattened beam characteristics, the Wilcoxon and Student's t tests for two paired samples were used to compare the plan metrics between 6FF-600 MU/min vs. 6FFF-600 MU/min and 6FF-600 MU/min vs. 6FF-1400 MU/min.

3. Results

For our patients' group, the mean and median GTV volumes were 6.9 cc and 3.3 cc, respectively. The mean and median ITV volumes were 13.2 cc and 9.3 cc with a range of 0.7–51.5 cc. After adding the margin to ITV, the created PTV volumes equalled 32.2 cc (mean) and 26.4 cc (median) with a range of 5.0–97.8 cc. The tumour position changes during the breathing cycle, described using PtP parameter, were dominant in the cranial-caudal axis with mean ± SD of 0.68 ± 0.57 cm (with a range of 0.15–1.99 cm). For the left-right and anterior-posterior directions, the PtP values were significantly smaller and equalled 0.20 ± 0.11 cm (0.03−0.37 cm) and 0.32 ± 0.18 cm (0.12−0.81 cm), respectively.

Finally, a total of 45 treatment plans were calculated using the VMAT technique (by means of RA) in the FFF mode and 15 with VMAT with the FF modality. The analysed plans were prepared with 2–6 arcs (both clockwise and counter-clockwise). Generally, the plans were utilized with median three coplanar arcs and with median sum of arcs rotational length of 340 degrees around the ipsilateral lung.[9] The maximum dose rate for plans created with the selected maximum dose rate feature was reached from the first analysed control point of each treatment plan's field and continued till the end without decreasing at any control point. The only exception was detected for the highest selected dose rate. For the radiation delivery with 1400 MU/min, in the case of 3 patients, the dose rate decrease was found for a single therapeutic field at the distance of 4.0 degrees (patient no. 1), 3.6 degrees (patient no. 5) and 5.1 degrees (patient no. 6).

Due to the results of pre-treatment verification, all VMAT lung SBRT plans passed the dosimetric accuracy criteria. The average score with standard deviation found for local 2%/3 mm equalled 96.90 ± 2.36% (with median value of 97.50%).

3.1. Number of monitor units and beam on time

The lowest number of monitor units was achieved for 6FF-600 MU/min plans (14/15 patients). Contrary, the highest number of monitor units was detected among 6FFF-600 MU/min (7/15 patients) and 6FFF-1000 MU/min (5/15 patients). In addition, in the case of another patient, the number of monitor units for 6FFF-600 MU/min and 6FFF-1000 MU/min plans was the same and at the same time it was the highest MU number compared to other plans. Exceptionally, in the case of the patient with the smallest ITV and, consequently, PTV volumes, the lowest number of MUs was found for 6FFF-1400 MU/min and the highest for 6FF-600 MU/min plan (Table 1). Taking into account the dose rate of the plan, the number of MUs was directly converted into beam on time. This recalculation revealed that 6FFF-1400 MUs/min plans were characterized by the shortest beam on time (1.8 ± 0.2 min). Comparing to the longest beam on time (4.30 ± 0.50 min) detected for 6FFF-600 MU/min, on average, the irradiation time for the 6FFF-1400 MUs/min plan was reduced by more than 58% (individually, it ranged between 57.0–63.5%). Comparing 6FFF-1400 MUs/min and 6FFF-1000 MUs/min (2.56 ± 0.33 min), approximately 30% of beam on time reduction could be found (with the range of 22.3%–39.1%) in favour of the larger dose rate. Although, in most cases, the number of monitor units was the lowest for 6FF-600 MU/min, the beam on time for this plan was only shorter than for 6FFF-600 MU/min, as specified in Table 1.

3.2. Changes of targets DVH metrics – descriptive statistics

The percentage values of means with the calculated standard deviations and minimum and maximum values detected among GTV, ITV, PTV and GTV0-100 for 6FF-600 MU/min, 6FFF-600 MU/min, 6FFF-1000 MU/min, 6FFF-1400 MU/min and 3

Table 1
Study population and treatment plan characteristics.

Pt no	Gender	Age	Fr dose [Gy]	Total dose [Gy]	Volume [cc]			Arcs no	The sum of arcs rotational length	Total MU				Beam on time			
					GTV	ITV	PTV			6FF-600	6FFF-600	6FFF-1000	6FFF-1400	6FF-600	6FFF-600	6FFF-1000	6FFF-1400
1	M	81	12.5	50	3.3	10.5	32.3	6	386	2414	2909	3000	2857	4.02	4.85	3.00	2.04
2	M	61	12.5	50	4.1	9.3	26.4	2	340	1974	2345	2273	2331	3.29	3.91	2.27	1.67
3	F	68	12.5	50	0.5	1.8	5.2	3	302	2375	2747	2750	2732	3.96	4.58	2.75	1.95
4	M	61	10	50	26.5	51.5	97.8	6	406	1587	2207	2035	2214	2.65	3.68	2.04	1.58
5	F	59	12	48	19.2	30.3	68.5	6	446	2221	2775	2775	2700	3.70	4.63	2.78	1.93
6	M	79	11	55	10.6	13.0	45.5	6	406	2341	2953	2851	2835	3.90	4.92	2.85	2.03
7	M	82	12	48	12.1	22.5	53.8	6	388	2308	2989	2987	2985	3.85	4.98	2.99	2.13
8	M	80	10	50	8.2	15.5	28.5	3	188	1818	2324	2289	2282	3.03	3.87	2.29	1.63
9	M	57	12	48	10.7	20.8	48.3	2	330	1717	2194	2196	2196	2.86	3.66	2.20	1.57
10	M	57	12	48	1.7	8.2	24.8	2	310	1728	2164	2080	2070	2.88	3.61	2.08	1.48
11	F	34	12	48	0.4	0.7	5.0	3	223	2146	2655	2653	2655	3.58	4.43	2.65	1.90
12	F	34	12	48	0.3	0.7	5.0	3	218	2424	2387	2386	2034	4.04	3.98	2.39	1.45
13	F	58	12	48	0.8	1.4	8.0	6	396	2326	2936	2941	2913	3.88	4.89	2.94	2.08
14	F	57	12	48	2.6	5.8	12.7	3	163	2106	2646	2629	2573	3.51	4.41	2.63	1.84
15	M	59	10	50	3.2	5.8	21.6	6	360	1938	2512	2515	2514	3.23	4.19	2.52	1.80
				Mean	6.94	13.19	32.22	4.20	324.13	2094.87	2582.87	2557.33	2526.07	3.49	4.30	2.56	1.80
				Median	3.30	9.30	26.40	3.00	340.00	2146.00	2646.00	2629.00	2573.00	3.58	4.41	2.63	1.84
				Maximum	26.50	51.50	97.80	6.00	446.00	2424.00	2989.00	3000.00	2985.00	4.04	4.98	3.00	2.13
				Minimum	0.30	0.70	5.00	2.00	163.00	1587.00	2164.00	2035.00	2034.00	2.65	3.61	2.04	1.45
				SD	7.47	13.29	25.71	1.72	85.47	273.00	287.63	319.17	306.70	0.45	0.48	0.32	0.22

versions of motion simulation were summarized in Supplementary materials.

3.2.1. Mean doses

The simulated impact of interplay between tumour motion, gantry rotation and MLC movement on final dose distribution during radiation delivery showed that no matter which DVH parameter (except PTV) was taken into account, its Dmean (averaged over 15 treatment plans performed with selected beam quality characteristics) was always higher than the reference dose (from original treatment plan). The detected percentage mean dose differences averaged for all plans were smaller at the beginning of the breathing period (meaning during maximum normal inspiration), then slightly increased towards bins identified as maximum normal expiration and, finally, went down to the other bins of the breathing curve. Nonetheless, for any respiratory phase and any kind of performed simulation, the mean dose differences among GTV0-100 did not exceed 1%. Similar dose mean values were found for GTV and ITV, whereas for PTV the perturbed dose mean averaged over all 15 cases was slightly smaller than the PTV reference plan dose. Taking into account the individual results, the percentage differences between the four groups of plans and three versions of motion simulation were similar.

3.2.2. Minimum doses

Considering the correlation between perturbed dose results and the breathing curve to find the local minimum values, the minimum perturbed doses showed a completely opposite tendency than the mean dose. No matter which simulation option and beam quality in the perturbed plan were used, the minimum perturbed doses averaged over all 15 cases, for bins at the beginning of the breathing curve (identified during this study as maximum normal inspiration), were burdened with about −1% difference from the reference planned dose. The above mentioned minimum doses tended to achieve values close to zero for bins towards expiration phases, and then the calculated numerical values were rising to initially detected values. The averaged minimum perturbed doses in GTV, ITV and PTV structures also proved to be lower than the reference minimum doses computed in the treatment planning system. While for this analysed parameter the percentage differences for GTV and ITV equalled no more than −1.05% and −1.35%, respectively, for PTV the revealed differences were significantly higher (on average up to −5.6%). Taking into account the individual results while analysing the minimum dose detected in PTV, maximal percentage differences equalled −18.98%, −18.62% and −18.02% for 1Ph, RanPh and StatMean simulations. Depending on the photon beam quality parameters used, the differences up to −17.16%, −18.98%, −18.93% and −12.74% at 6FF-600 MU/min, 6FFF-600 MU/min, 6FFF-1000 MU/min and 6FFF-1400 MU/min for PTV occurred in one patient (patient no. 4). Insightful analysis suggested that the detected differences were significantly associated with the impact of plan dose rate and tumour size (the highest GTV, ITV and, consequently, PTV among the selected patients' cohort).

3.2.3. Maximum doses

Looking for local maximum, no matter for which structure, the dose parameter averaged over all fractions was verified, the perturbed relative dose (regardless of the simulation performed) was higher than the reference plan dose mainly up to 2%. Considering the above mentioned maximum values averaged over all plans, the tendency was noticed that, mostly among 6FF-600 MU/min results, the highest local overdosage was found independently of performed simulation.

Table 2
The statistically significant differences detected between planned and simulated dose data among 1 Phase (1Ph), Random Phases (RanPh) and Statistical Mean (StatMean) motion simulation data and 6FF-600 MU/min, 6FFF-600 MU/min, 6FFF-1000 MU/min and 6FFF-1400 MU/min treatment plans.

Motion simulation method	Dose metrics	Structure	p-Value
1Ph	Dmin	GTV10	0.027
		GTV20	0.047
		GTV30	0.040
		GTV40	0.047
		GTV50	0.032
		GTV80	0.036
		GTV90	0.028
		GTV100	0.049
RanPh	Dmin	GTV90	0.001
	Dmax	GTV30	0.028
		GTV70	0.038
StatMean	Dmin	GTV90	0.003
	Dmax	GTV20	0.047
	Dmean	GTV20	0.044
		GTV30	0.032
		GTV40	0.019
		GTV50	0.047

Table 3
The statistically significant differences detected between planned and simulated dose data among 1 Phase (1Ph), Random Phases (RanPh) and Statistical Mean (StatMean) motion simulation data and between 6FF-600 MU/min against 6FFF-600 MU/min and 6FFF-1400 MU/min treatment plans.

Motion simulation method	Dose metrics	Structure	p-Value
6FF-600 MU/min vs. 6FFF-600 MU/min			
1Ph	Dmin	GTV10	0.030
		GTV70	0.041
		GTV90	0.008
RanPh	Dmin	GTV70	0.046
	Dmax	GTV	0.011
		ITV	0.008
		PTV	0.030
		GTV20	0.031
		GTV30	0.009
		GTV60	0.048
		GTV70	0.030
	Dmean	ITV	0.044
		GTV10	0.048
		GTV20	0.044
		GTV30	0.048
		GTV40	0.041
		GTV50	0.041
		GTV70	0.035
StatMean	Dmin	GTV70	0.046
		GTV90	0.007
	Dmax	GTV	0.016
		ITV	0.048
		GTV20	0.013
		GTV30	0.019
		GTV60	0.035
		GTV70	0.026
	Dmean	GTV	0.019
		ITV	0.041
		GTV20	0.010
		GTV30	0.015
		GTV40	0.008
		GTV50	0.016
		GTV60	0.019
		GTV70	0.030
6FF-600 MU/min vs. 6FFF-1400 MU/min			
1Ph	Dmin	GTV0	0.036
		GTV30	0.006
		GTV40	0.035
		GTV50	0.031
StatMean	Dmin	GTV90	0.035

3.2.4. D95%, D95%, D99%

Among D95% for GTV, ITV, PTV and 3 kinds of simulations, the noticed differences could be neglected, whereas for D98%, mainly the differences between reference and perturbated doses were found for 6FFF-1400 MU/min while performing 1Ph simulation and for 6FF-600 MU/min after analysing RanPh and StatMean simulation results. It is worth underlining that sampling density increase did not change significantly the observed D98% dose differences among RanPh and StatMean simulations. The same tendency as for D98% was also observed for D99% (only small, insignificant fluctuations within PTV between RanPh and StatMean were detected).

3.2.5. Standard deviations

Finally, no matter which structure and dose metrics parameter was analysed, the tendency was noticed that among 1Ph simulation results, the SD parameter took the highest values mainly for 6FFF-1400 MU/min. According to the results of the two other kinds of simulation (RanPh and StatMean), the standard deviation observed for 6FF-600 MU/min tended to be dominant.

3.3. Changes of targets DVH metrics – statistical analysis

According to the results of performed statistical testing, the effect of motion was predominant among 1 Phase (1Ph) simulation data. The statistically significant findings from the presented data were summarized in Table 2. The simulated perturbation revealed the statistically significant differences between 6FF-600 MU/min, 6FFF-600 MU/min, 6FFF-1000 MU/min and 6FFF-1400 MU/min minimum dose differences for GTV10, GTV20, GTV30, GTV40, GTV50, GTV80, GTV90 and GTV100. All those means were characterized by negative values, which meant that the simulated dose was lower than planned. As presented in Supplementary materials, the highest discrepancies of means among Dmin and 1Ph simulation were detected while 6FFF-1400 MU/min plans were perturbed. The results averaged for all 15 observations showed that the highest detected discrepancies of Dmin for GTV100 reached nearly −1.7%. Unfortunately, for extreme cases the differences found between perturbed and planned doses reached more than −6.5%. The second version of motion simulation (RanPh) revealed statistically significant differences between 6FF-600 MU/min, 6FFF-600 MU/min, 6FFF-1000 MU/min and 6FFF-1400 MU/min plans among the following parameters: GTV90 Dmin, GTV30 Dmax and GTV70 Dmax, whereas for StatMean simulation, statistically proved differences were detected for GTV90 Dmin, GTV20 Dmax and GTV20-GTV50 Dmean.

Comparison between 6FF-600 MU/min against 6FFF-600 MU/min and 6FFF-1400 MU/min plan results highlighted a lot of statistically significant differences, in particular between flattened and unflattened beams with the same dose rate while performing RanPh and StatMean simulations. Precisely, the detected differences were found mainly between Dmax and Dmean plan parameters. In contrast to the results of this part of the analysis, a comparison of 6FF-600 MU/min vs. 6FFF-1400 MU/min showed almost no differences for RanPh and StatMean simulations' types and single statistically significant results while 1Ph perturbation was simulated (Table 3).

The differences between the additional DVH metrics (D95%, D98% and D99%) defined for GTV, ITV and PTV were insignificant among all simulation results for all plans' beam quality parameters.

4. Discussion

This study was designed to demonstrate the benefits and drawbacks of using different photon beam quality parameters for VMAT

lung SBRT and to evaluate the robustness of the VMAT FF vs. FFF concepts against so-called interplay effects. Thus, at the first step, four different external beam radiation therapy plans were computed in the treatment planning system (6FF-600 MU/min; 6FFF-600 MU/min; 6FFF-1000 MU/min; 6FFF-1400 MU/min). As by removing the flattening filter, the linear accelerator generates a beam characterized by a very high dose rate on the central beam axis, with rapidly decreasing intensity moving away from the beam centre, FFF fields seem to be dedicated to stereotactic procedures. Nonetheless, while performing the assumptions of the presented study, the authors decided to compare both flattened and unflattened fields to show the whole spectrum of possible clinical results achieved for 6 MV photon beam quality. Additionally, the results of this broad analysis may be important for smaller oncology centres without FFF beams. At first step, it turned out that in all four versions of treatment plans computed for 15 patients, taking into account both the targets (GTV, GTV0-100, ITV and PTV) coverage and dose distribution data calculated for OARs, all objectives were met. From this point of view, there was no limitation to create the plan for VMAT lung SBRT. Although the dosimetric quality assurance of 6FF-600 MU/min plans tended to achieve the lowest accuracy results, it was still above the imposed criteria contained in our VMAT lung SBRT clinical procedure, which are in line with published data and guidelines.

4.1. Motion simulation

Then, three different software simulations of the accumulated dose in the moving tumour were performed based on a tumour motion cycle. During the first simulation process, the dose delivery always started with maximum normal inspiration, whereas during the second simulation calculation, the randomly chosen breathing phase was selected. Finally, for the third kind of simulation, the sampling density of 10 was used to verify the manufacturer statement that this sampling density averages out the impact of motion during VMAT radiation delivery. The above simulation results demonstrated that the interplay effects during 6FF-600 MU/min; 6FFF-600 MU/min; 6FFF-1000 MU/min and 6FFF-1400 MU/min VMAT lung SBRT had a similar influence on the target dose coverage. The insightful analysis enabled us to conclude that for VMAT lung SBRT the mean dose (Dmean) is not a sensitive parameter to related interplay effects. The percentage Dmean differences between simulated plans and the reference plans computed in the treatment planning system for analysed DVH parameters were so discrete that, generally, they had no power to reveal any significant motion effects. The differences detected while comparing 6FF-600 MU/min vs. 6FFF-600 MU/min, in our opinion, were associated with beam characteristics (flattened vs. unflattened fields). Adding the dose rate components to the performed analysis eliminates the significance of achieved differences even for flattened vs. unflattened data sets (as was presented while comparing 6FF-600 MU/min vs. 6FFF-1400 MU/min data).

Looking for local maximum and local minimum, which are often reported in literature as possible critical values, we found some discrepancies but their significance was presented for individual patients, not for the whole cohort. Depending on the way of performing motion simulation, generally, effects of motion were dominant among 6FFF-1400 MU/min plans (according to 1Ph simulation) or 6FF-600 MU/min plans (while RanPh and StatMean results were analysed). The tendency was that the changes in dose perturbation assumptions from maximum normal inspiration (as was the case for 1Ph simulation) to random phases (for RanPh and StatMean) exposed the values responsible for the main differences for 6FF-600 MU/min. Additionally, the DVH metrics (D95%, D98%, D99%) used did not add any statistically significant results. Especially, for D98% and D99%, the same tendency as for Dmin and Dmax was found, namely that randomly selected simulation phases exposed the values responsible for the main observed differences between reference plans and simulation results for 6FF-600 MU/min. Analyzing the achieved results in terms of statistically significant differences, it was found that the impact of using different photon beam quality parameters (FF vs. FFF beams and dose rate of 600 MU/min, 1000 MU/min and 1400 MU/min) was minimal. Detected statistically significant impact of chosen photon beam quality was always found for GTV parts associated with a direct tumour location in a given respiratory phase. For 1Ph simulation results, all revealed statistically significant differences were detected for Dmin. The RanPh demonstrated the statistically significant differences for single GTV parts among Dmin and Dmax. Finally, the StatMean simulation results showed statistical differences among four groups of plans not only for Dmin and Dmax, but also for Dmean among selected GTV parts. Additionally, we found two regularities connected with dose difference analysis for GTV0-100. The first was that the detected percentage mean dose differences averaged for all plans were smaller at the beginning of the breathing period (identified as maximum normal inspiration), then slightly increased towards bins identified as maximum normal expiration and finally went down to the other bins of the breathing curve. The other was connected with the fact that the minimum perturbed doses averaged over all 15 cases for bins at the beginning of the breathing curve were burdened with a difference of about −1% compared to the reference planned dose. The above mentioned minimum doses tended to achieve the values close to zero for bins towards the expiration phases (almost 100% agreement between the planned and simulated dose) and then the calculated numerical values rose to initially detected values. The insightful reader may ask how it is possible for ITV-based delivery, when the breathing motion margin was encompassed in the ITV structure and all other possible errors (residual and setup ones) were included in a 5-mm isotropic ITV to PTV extension.[33] Due to the nature of ITV creation, the peak to peak (PtP) motion was chosen to inform about the changes of the tumour centre of gravity location during one breathing cycle. Analysing PtP results in the left-right, cranial-caudal and anterior-posterior directions we found no tendency that for patients with higher PtP values the higher dose discrepancies among planned and simulated data were detected. Trying to answer the question about this phenomenon we found Gauer et al.[3] study in which authors underlined the nature of observed interplay effects. According to them, interplay effects cannot be closed within just respiration-induced tumour movement and fluence, gantry and MLC motion. All of these variables could be described using more specific parameters: tumour size, location and motion characterized by period, amplitude, degree of freedom or phase shift. As also presented above comparing the simulation results, the tumour location at the start of dose delivery, as well as dose rate cannot be neglected. As regards technical parameters, also speed of leaf motion or size and shape of MLC openings had an impact on observed dose distribution differences due to interplay effects.[3] That is why, Hrbacek et al.[8] underlined that especially in cases where FFF beams are combined with dynamic techniques, comparative plan analysis as well as beam comparison is not a trivial task.

Larger discrepancies (but still for each tested photon beam quality and all simulations performed) were observed for the PTV structure. Precisely, the results from the performed simulations are in agreement with previously published study by Zou et al.[9] Based on simulating dynamic dose delivery using dynamic CT datasets, they generally demonstrated the limited effect of motion during the VMAT lung SBRT of 12.5 Gy per fraction. What is interesting, they concluded that small dose differences appeared within the PTV, while finding larger dose deviations at the superior and inferior borders outside the PTV. As demonstrated, it was due to the

fact that superior and inferior regions outside the PTV were only irradiated at some phases of the breathing cycle which is in line with our observations.

4.2. Treatment time

The next important factor is connected with treatment time, which was one of the factors evaluated in this study. Analysing the plans in terms of monitor units and beam on time, first of all, the highest number of monitor units was detected mainly among 6FFF-600 MU/min and 6FFF-1000 MU/min. The lowest number was revealed for 6FF-600 MU/min. The translation of MU number into beam on time changed this tendency. Due to the high dose rate, the beam on time was the shortest for 6FFF-1400 MU/min and the longest for 6FFF-600 MU/min. Trying to translate this results into possible interplay effects, which they can cause, on one hand, there are repetitive investigation findings that the interplay effects are less pronounced with longer delivery times and other treatment related parameters like larger number of fractions or multiple fields/arcs,[3] while, on the other hand, it was proved that the daily treatment time could not be neglected. Due to the reported intrafraction lung SBRT results, the probability as well as the size of the tumour displacement increased for longer delivery times while the displacement was compared between initial patient positioning and the end of daily treatment.[15] The regularity described in literature demonstrated that for lung patients groups the systematic geometric error resulting from intrafraction movements increases linearly with time.[34] In clinical settings it means that during a treatment fraction the patient slowly drifts away from his or her initial position despite immobilization techniques applied. It is worth mentioning here that the recently published data reported the lack of dependence between immobilization devices used and tumour respiratory-induced motion.[4]

4.3. Treatment planning issues

Of course, the achieved results cannot be interpreted without reference to the study assumptions and its conditions leaving room for discussing the different parameters of computed treatment plans. For example, with our treatment planning assumptions (arcs rotational length limited to the ipsilateral lung with simultaneous avoidance of arm) the number of arcs used may be disputable. Thus, we found the study published by Barrett et al.[35] demonstrated that the number of arcs did not statistically correlate with the dose changes observed for different structures (both tumour and OARs) when the VMAT technique was used for peripheral lung SBRT.

4.4. Study limitations

The presented study was limited to the analysis of tumour dose distribution changes. This was in line with literature results indicating that for tumour locations for which OARs were not in close proximity, there was no concern about reaching or exceeding the dose limits.[35] For the 15 selected clinical cases, the approved treatment plans reported the OARs doses well below established constraints due to their being located far from the tumour. Undoubtedly, a lot of attention should be paid when treating the lung tumour located proximal to any OARs because for such patients the motion and, consequently, interplay effects would have a significant impact.[9]

The study methodology could raise some concern not only about tumour respiratory motion reproducibility, but also about its regularity during treatment delivery.[4,9] Zou et al. defined two main sources of errors while applying the ITV-based lung SBRT approach. These were artifacts due to irregular breathing while performing 4DCT and accuracy of the target motion envelope from a single 4DCT reconstruction. The first affected the precision in defining the tumour volume and its location, while the other may change the target coverage.[9] Based on our clinical practice, we put emphasis on a breathing training method to eliminate any significant cycle-to-cycle variations. Finally, only when the reproducible pattern of respiration is observed, the scanning procedure starts.[4] Then, during radiation delivery, pre-treatment image guidance is necessary to verify the accuracy and reproducibility of single 4DCT-based tumour motion envelope.

Analysing the study results and performing their statistical approach, one should remember that it is not possible to eliminate the whole "treatment process" bias to finally achieve (with each optimization) clinically acceptable plans. Focusing on the study methodology, some uncertainties were also introduced due to images, plan and dose export from Eclipse, their import to 3DVH software and perturbed dose calculation, although during all dose computations (both in Eclipse and 3DVH) the fine calculation grid was used to optimize accuracy.

The last but not the least point is connected with the ITV reconstruction method. Recently, the ITV approach described in this article has been reported as the dominant motion compensation practice used in majority of radiotherapy centres.[23] Due to the fact that according the ITV method breathing motion is a systematic error, it takes into account the full extent of tumour motion to the margin. On the other hand, mid ventilation (Mid-V) or mid projection (Mid-P) methods treat breathing motion as a random error for the purpose of PTV margin calculation, finally giving smaller treatment volumes to irradiate. Thus, the results of the presented study cannot be directly transformed into the effects observed during flattened and unflattened Mid-V or Mid-P based VMAT lung SBRT.

5. Conclusions

This study demonstrated the benefits and drawbacks of using different photon beam quality parameters for ITV-based VMAT lung SBRT. Generally, the evaluation of VMAT robustness between FF and FFF concepts against the interplay effect showed a negligible effect of simulated motion influence on tumour coverage among different photon beam quality parameters. The significance of the discrepancies found was presented for individual patients, not for the whole cohort. Based on performed motion simulations, which quantified the interplay effect impact on final dose distribution, under idealized conditions (when the irradiation will always start with the same breathing phase) the highest agreement between planned and simulated dose was achieved for 6FF-600 MU/min treatment plans. Simulations performed with motion perturbing all fractions with random phases changed this tendency into 6FFF-1400 MU/min photon beam quality. Additionally, according to the achieved results, the 6FFF-1400 MU/min treatment plans enable to reduce the patients beam on time. The important finding of the study is that due to the lack of FFF beams, smaller radiotherapy centres are able to perform ITV-based VMAT lung SBRT treatment in a safe way. Radiotherapy department having FFF beams could perform safe, fast and efficient ITV-based VMAT lung SBRT without a concern about the significance of interplay effects among the respiration-induced tumour movement, fluence, gantry and MLC motion due to shortening the irradiation time.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rpor.2020.06.003.

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