

research article

Verification of an optimizer algorithm by the beam delivery evaluation of intensity-modulated arc therapy plans

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Radiol Oncol 2021; 55(4): 508-515.

Received 25 June 2021

Accepted 17 August 2021

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Disclosure: No potential conflicts of interest were disclosed

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Background. In the case of dynamic radiotherapy plans, the fractionation schemes can have dosimetric effects. Our goal was to define the effect of the fraction dose on the plan quality and the beam delivery.

Materials and methods. Treatment plans were created for 5 early-stage lung cancer patients with different dose schedules. The planned total dose was 60 Gy, fraction dose was 2 Gy, 3 Gy, 5 Gy, 12 Gy and 20 Gy. Additionally renormalized plans were created by changing the prescribed fraction dose after optimization. The dosimetric parameters and the beam delivery parameters were collected to define the plan quality and the complexity of the treatment plans. The accuracy of dose delivery was verified with dose measurements using electronic portal imaging device (EPID).

Results. The plan quality was independent from the used fractionation scheme. The fraction dose could be changed safely after the optimization, the delivery accuracy of the treatment plans with changed prescribed dose was not lower. According to EPID based measurements, the high fraction dose and dose rate caused the saturation of the detector, which lowered the gamma passing rate. The aperture complexity score, the gantry speed and the dose rate changes were not predicting factors for the gamma passing rate values.

Conclusions. The plan quality and the delivery accuracy are independent from the fraction dose, moreover the fraction dose can be changed safely after the dose optimization. The saturation effect of the EPID has to be considered when the action limits of the quality assurance system are defined.

Key words: treatment planning system; fractionation scheme; dose optimization; plan normalization

Introduction

Lung cancer is one of the leading causes of cancer death in the world.¹ An early diagnosed non-small cell lung cancer (NSCLC) patient nowadays has a chance for longer survival, because of the emerging treatment techniques. In radiotherapy the rapid technical development allows to perform more effective treatments using higher doses for better tu-

mor control. The standard radiotherapy treatment for patients was carried out by applying only a total dose of 60 Gy with 2 Gy per fraction (biological effective dose $BED_{10} = 72$ Gy). The stereotactic body radiation therapy (SBRT) is the standard radiation treatment for early stage, nodal negative lung cancer that can be irradiated with up to 60 Gy in 3 fractions ($BED_{10} = 180$ Gy).²⁻⁵ The local tumor control of SBRT treatments is comparable with the surgical

resection, and can be performed also for patients judged inoperable due to other comorbidities.⁶⁻⁹

The dose prescription according to recommendations has to be risk adapted, and the size and location of tumor influence the maximum deliverable doses; that way fractionation schemes are used multifariously as well as the daily fraction dose.¹⁰⁻¹⁶

During SBRT planning the main goal is to reach high dose conformity and steep dose gradient around the target volume to spare the dose to the organs at risk. In case of stereotactic treatments to ensure acceptable dose gradient, there is a dose prescription for an isodose line (IDL), and with this method, steeper dose fall-off can be achieved in return for higher dose maximum.¹⁷⁻²¹ Many studies recommend various methods for the optimal selection of the prescribed IDL.²²⁻²⁴

Earlier, in the era of static fields, delivery discrepancies were not caused by the change of the prescribed IDL in clinical practice. SBRT techniques are performed with intensity modulated dynamic fields²⁵ and in this case if the original fraction dose or the prescribed IDL is changed, the delivery parameters are modified - compared to the original optimized ones - which can have an effect on the accuracy of beam delivery.

The uncertainties in radiotherapy are widely presented in the literature, but the effect of the fraction dose value has not been examined deeply.²⁶ In our experience, discrepancies can be caused in the operation of the optimizer by the application of extremely low or high fraction dose values (e.g. few cGy). The aim of our work is to compare plan quality and the deliverability of radiotherapy treatment plans with different dose per fraction values used in clinical practice. We have examined the effect of changing the normalization values from the original optimized ones to other dose per fraction values. The potential pitfalls of the variation of the dose per fraction values were also determined.

Materials and methods

Case selection

Five lung SBRT patients were selected for the study and a set of treatment plans with various parameters were created. 4D CT scan was performed for all patients with a Siemens Definition AS Open (Siemens AG, Erlangen, Germany) scanner and the breathing motion was monitored using the adjustable belt of AZ-733V (Anzai Medical, Tokyo, Japan). The scan parameters were based on the clinically used protocol with 120 kVp without kV modulation, and 2 mm slice thickness. According to the breathing pattern 7 (+1 average) image sets were created with retrospective reconstruction. For target definition the internal target volume (ITV) concept was used. The radiation oncologist delineated the gross tumor volume (GTV) on each of the 7 image sets. No margin was applied between the GTV and the clinical target volume (CTV). The accumulated GTV was created on the average CT and 5 mm additional margin was used to create the planning target volume (PTV). All of the lesions were peripheral, at least 1 cm from the rib cage and mediastinum. During the selection we have strived to create a heterogeneous group, the parameters of the patients and the targets can be found in Table 1.

Treatment planning

5 different fractionation schemes were defined for all patients, 60 Gy total dose with 2, 3, 6, 12, and 20 Gy fraction dose, that way the number of fractions were 30, 20, 12, 5 and 3, respectively. The treatment plans were created with Eclipse 13.6 treatment planning system's Photon Optimizer 13.6 algorithm (Varian Medical Systems, Palo Alto, CA, USA), and delivered on a TrueBeam (Varian Medical Systems, Palo Alto, CA, USA) machine. The isocenter was placed in the geometrical center of the PTV, 4 restricted arcs were defined using 6 MV-flattening

TABLE 1. The parameters of the selected patients and irradiated volumes

Sex	Age [years]	Lobe	GTV_volume [ccm]	Tumor movement [mm]	ITV_volume [ccm]	PTV_volume [ccm]
Male	84	Right-lower	3.7	20	10.7	33.3
Male	66	Left-upper	1.3	4	2.2	11.5
Male	72	Left-upper	4.8	5	7.2	24.9
Female	61	Right-mid	2.6	4	3.9	15.1
Female	67	Right-mid	0.7	2	1.1	7.6

GTV = gross tumor volume; ITV = internal target volume; PTV = planning target volume

TABLE 2. The mean values and the standard deviations of the plan quality parameters

	2 Gy/fraction	3 Gy/fraction	6 Gy/fraction	12 Gy/fraction	20 Gy/fraction
PTV_D _{mean} (cGy)	6706±96	6713±85	6701±97	6715±91	6686±96
PTV_V95 (%)	98.17±2.34	98.44±1.61	98.32±1.72	98.43±1.67	98.22±1.93
PTV_V100 (%)	91.12±5.29	91.85±4.34	91.31±4.63	91.82±4.54	90.78±4.93
PTV_V98 (%)	94.9±4.24	95.47±3.28	94.97±3.54	95.39±3.48	94.75±3.84
PTV_D98 (cGy)	5759±141	5771±116	5760±128	5773±126	5755±128
PTV_D50 (cGy)	6749±128	6762±107	6750±125	6760±119	6726±125
PTV_D2 (cGy)	7515±114	7472±94	7461±106	7487±91	7454±87
ITV_D _{mean} (cGy)	7234±150	7229±126	7113±301	7124±262	7106±272
ITV_D98 (cGy)	6867±130	6901±101	6862±152	6877±125	6848±144
ITV_D50 (cGy)	7242±154	7229±134	7221±145	7238±117	7219±105
ITV_D2 (cGy)	7581±164	7556±162	7531±150	7561±142	7539±166
BODY_V100 (ccm)	17.1±9.56	17.25±9.64	17.13±9.66	17.24±9.72	17.16±9.57
BODY_V50 (ccm)	75.02±35.16	75.09±35.17	74.96±35.68	75.31±35.79	74.74±35.45
BODY_V98 (ccm)	18.2±10.03	18.34±10.11	18.22±10.13	18.34±10.19	18.1±10.16
D _{max} (cGy)	7816±128	7777±106	7731±106	7794±16	7691±288
Lung_V5Gy (%)	15.57±7.25	15.51±7.31	15.59±7.24	15.57±7.3	15.56±7.26
Lung_V20Gy (%)	4.25±2.32	4.28±2.33	4.25±2.33	4.27±2.34	4.26±2.34
Lung_D _{mean} (cGy)	342±148	343±149	342±149	343±149	342±149
# MU / cGy	2.84±0.15	2.81±0.1	2.8±0.12	2.81±0.11	2.81±0.12
R50%	4.27±0.52	4.27±0.51	4.25±0.51	4.27±0.5	4.24±0.49
CI98%_PTV	0.93±0.06	0.94±0.05	0.93±0.06	0.94±0.05	0.94±0.06
CN98%_PTV	0.9±0.03	0.91±0.02	0.91±0.02	0.91±0.02	0.91±0.03

CI = conformity index; CN = conformity number; ITV = internal target volume; MU = monitor units; PTV = planning target volume; R50% = calculated dose gradient

filter-free (FFF) energy and the maximal (1400 MU/min) dose rate. The primary jaws were fitted with 5 mm margin to the PTV, the jaw tracking was enabled. The final dose was calculated by AcurosXB algorithm with dose-to-water setting and 0.125 cm grid size. The optimization parameters were different patient by patient, but were kept the same between the different fractionations. The final results of optimizations were not changed, the minimum PTV coverage was V95% > 99 % and V98% > 95%, and the dose to organs at risk had to be fit for clinically used limitations, based on the European Organization for Research and Treatment of Cancer (EORTC) recommendations¹¹. After that, the original optimized plans were copied and the prescribed doses were changed for all the 4 other values. This way every patient had 25 different plans with 5 different fractionation schemes.

Data collection

For every plan the PTV coverage parameters were evaluated. The dose to the lung and the whole-

body volume were also examined. The statistical analysis of plan quality was performed with GraphPad 8.0.1 (GraphPad Software, San Diego, CA) using ANOVA and post-hoc Dunn's test. The delivery parameters such as the number of monitor units (MU), gantry speed and dose rate values were also collected. To characterize the multi-leaf collimator (MLC) motions aperture complexity metric (ACM) was determined for all beams by using a homemade software, according to the definition of Younge *et al.*²⁷ The score was calculated as:

$$ACM = \frac{1}{MU} \sum_{i=1}^N MU_i \times \frac{y_i}{A_i}$$

whereas

- MU is the total number of MUs in the plan,
- i = 1 to N control point apertures,
- MU_i is the number of MU delivered through aperture i,
- A_i is the open area of aperture i,
- y_i is the aperture perimeter excluding the MLC leaf ends,

and to calculate the score of a given arc, the metrics of all apertures have to be summed.

To evaluate the deliverability of the treatment plans, electronic portal imaging device (EPID) based dose measurement was performed with the portal dosimetry system using Portal Dose Image Prediction (PDIP) 13.6 algorithm (Varian Medical Systems, Palo Alto, CA, USA). The linear accelerator was equipped with an aS1200 Digital Megavolt Imager. Just before the measurements the linear accelerator and the EPID absolute were calibrated to ensure the most accurate results. The gamma analysis was performed for the 500 arcs in absolute mode with 2%, 1 mm parameters, 10% threshold, and the auto alignment was allowed. The maximum and central axis calibrated unit (CU) values of portal dose predictions and measurements were also collected and evaluated.

The meaning of phrases used in the Results section:

- Optimization dose: The dose per fraction value set before (during) the optimization.
- Normalization dose: The dose per fraction value set after the optimization.
- Optimized plan: The optimization dose and the normalization dose are equal.
- Renormalized plans: The optimization dose and the normalization dose are different.

Results

Renormalization does not change the *dose-volume histogram* (DVH) parameters compared to optimized plans. That way for the comparison of the

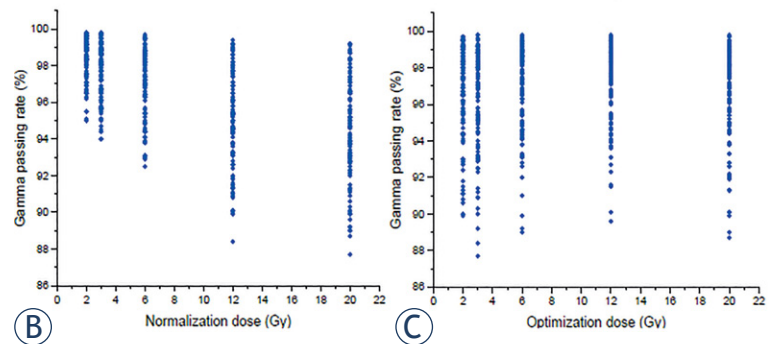
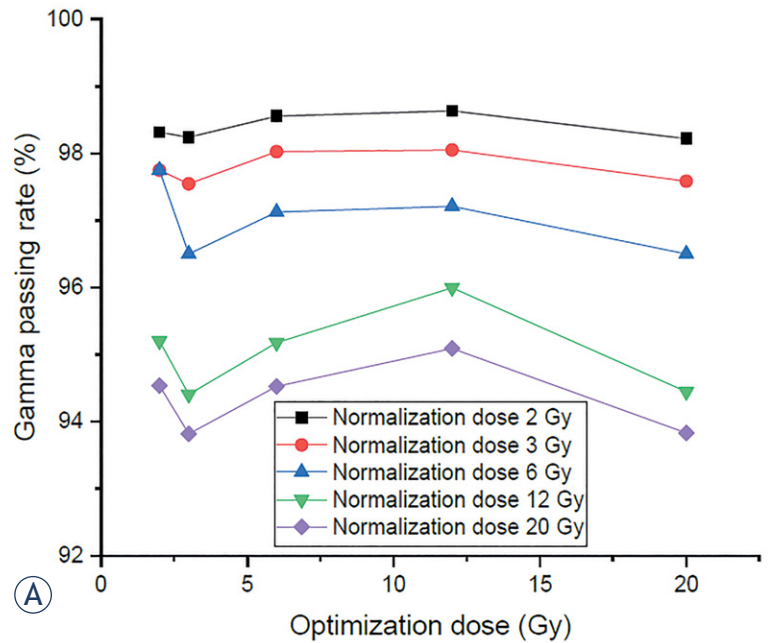


FIGURE 1. (A) The average value of gamma passing rates according to the used optimization separated by normalization, and the gamma passing rates according to the normalization (B) and optimization (C) dose values.

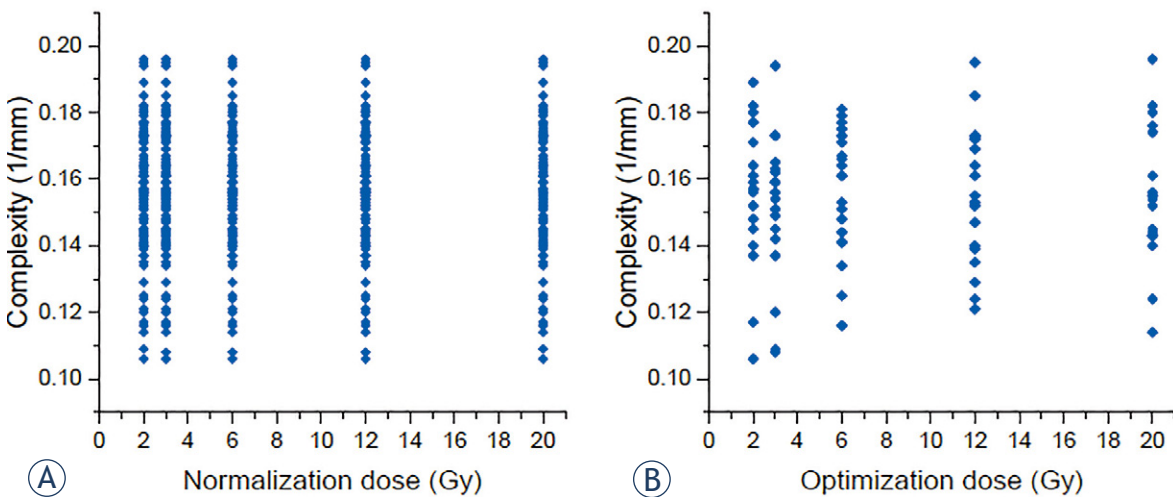


FIGURE 2. The effect of the normalization dose (A) and the optimization dose (B) values on the aperture complexity metric (ACM) score.

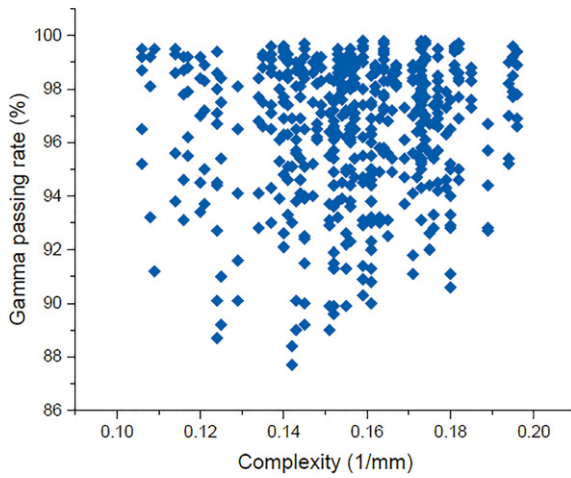


FIGURE 3. The connection between the complexity score and the gamma passing rate.

plan quality metrics, only the optimized plans have to be included. We compared the mean values of the dosimetric parameters of the five patients. PTV and ITV coverage parameters, dose to

lung and whole body parameters were evaluated.²⁸ Conformity index (CI) and conformity number (CN) were calculated for the PTV.²⁹ The dose gradient was described by R50% which is calculated as the ratio of the volume enclosed by the 50% isodose surface and the volume of the PTV.²⁹ There was no significant difference between any of the daily fraction size plans. The average values and the standard deviations of the parameters are summarized in Table 2. Based on the statistical tests, there was no significant difference between the optimization schedules.

The dependence of gamma values on the optimization and the normalization dose values were also investigated. Figure 1 presents that the gamma passing rates are independent from the optimization values, renormalization has no effect on the results. However, the higher fraction dose reduces the passing rates, independently of the used original optimization dose value.

Figure 2A indicates that the renormalization has no effect on the MLC motions. This can be concluded from the same pattern of ACM scores for differ-

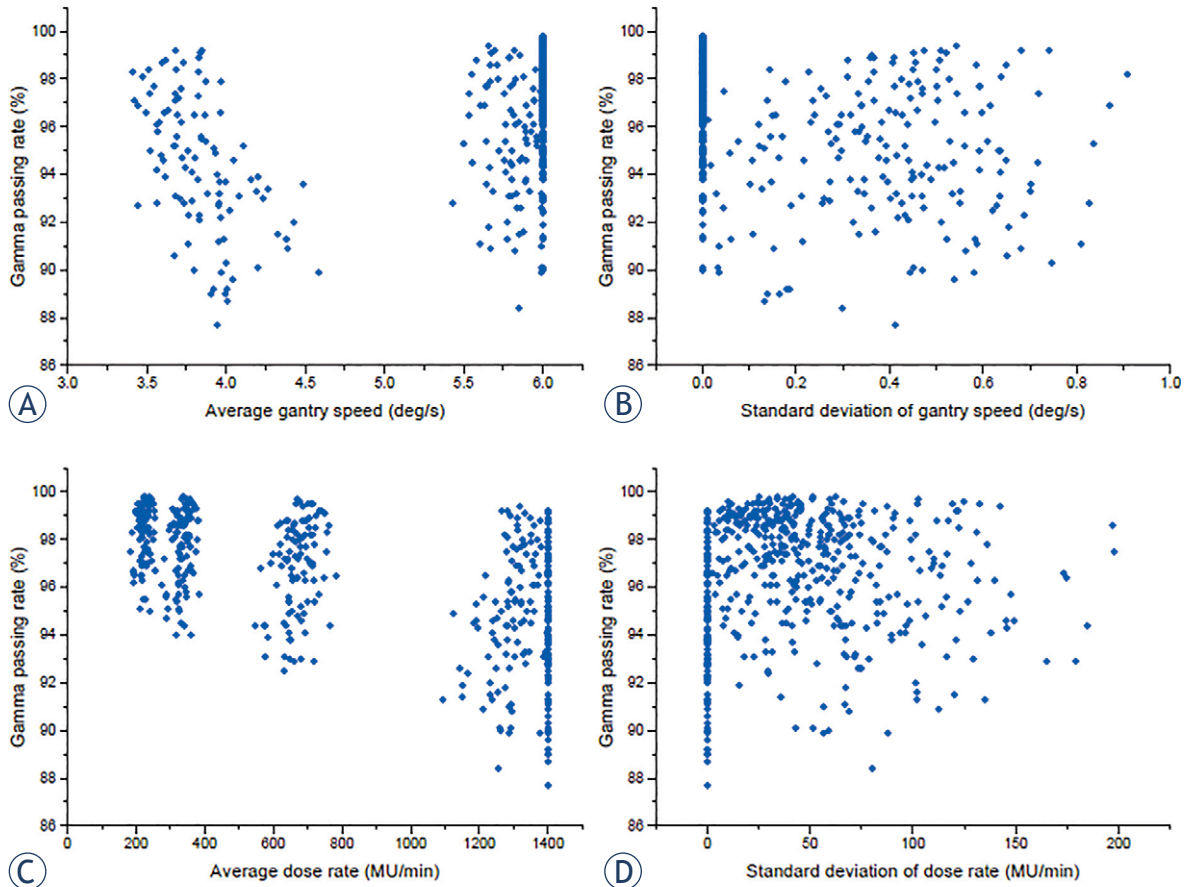


FIGURE 4. The effect of the average gantry speed (A) and standard deviation (B), and the average dose rate (C) and standard deviation (D) on the gamma passing rates.

ent normalization doses. Only the speed of delivery (gantry speed and dose rate) is changed with renormalization. According to Figure 2B, there is no connection between the optimization dose and the complexity metric.

The implementation of the calculated dose maps has no crucial effect on the accuracy of delivery. The optimizer tries to maximize the gantry speed and the enabled dose rate. For higher dose per fraction cases these limits are reached, which can be concluded from the constant mean and zero standard deviation values. In case of high MLC modulation, it is necessary to lower the speed of the delivery. The deviations of gantry speed and dose rate can be used as the describing parameters of the modulation of delivery. According to our data ACM, gantry speed and dose rate values do not correlate with gamma passing rates, as shown in Figure 3 and 4.

The predicted and measured CU values were separately evaluated to define the origin of the differences at high fraction dose. As Figure 5 shows, the deviation of predicted values is low, the CU/Gy values are quasi constant with the changing fraction dose. Meanwhile the measured maximum and the central-axis values are decreasing with the increasing fraction dose, which means the detector has a saturation effect.

Discussion

As can be shown in Table 2, the different optimization fractional dose has no significant effect on plan quality. To our knowledge, this is the first study to examine the effect of prescription dose on the plan quality for volumetric modulated radiotherapy treatment plans.

Figure 1 shows that the accuracy of the beam delivery does not change after changing normalization values. According to average gamma passing rate values there was a slight trend for reducing passing rates compared to the original optimization in case of the renormalization of 5 times 12 Gy plans. In case of 3 Gy per fraction the average gamma values were higher after renormalization. The data was analyzed even patient by patient, but we did not find any trend. As can be seen more clearly in Figure 1B, the higher fraction doses are decreasing, meanwhile the used optimization dose has no well-defined effect on the gamma passing rates, as can be seen in Figure 1C. The lower passing rates in case of high fraction dose can be caused by the limitation of the EPID detection for high dose levels.

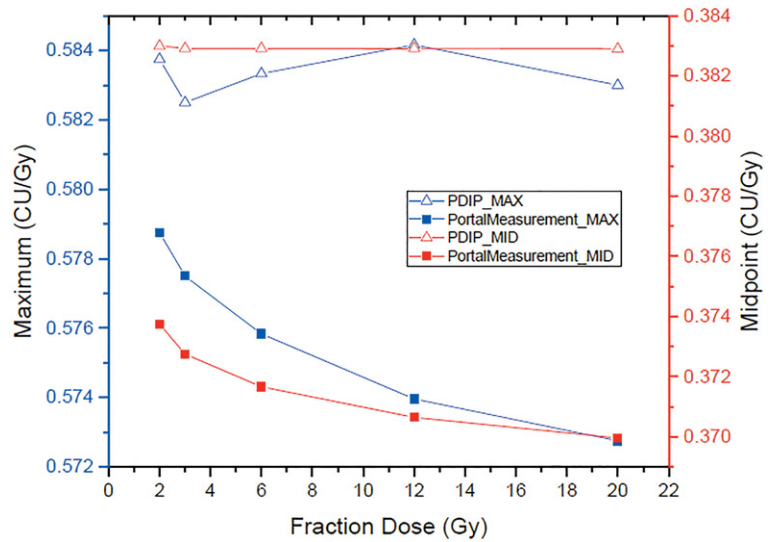


FIGURE 5. The predicted and measured number of maximum (blue) and the central-axis (red) calibrated units (CU) for 1 Gy according to the fraction dose.

PDIP = portal dose image prediction;

This saturation effect is more expressed than the impact of changing fraction dose. Former studies have verified the usability of the Portal Dosimetry system by testing the EPID based dose measurements.³⁰⁻³² Barbeiro *et al.* have demonstrated with synthetic tests that a slight decrease in response linearity can be observed at the high exposures with FFF beams.³³ Xu *et al.* found that the detector panel has a saturation in case of high dose-rate beams, but it was clinically insignificant even at the maximum dose rate of 2400 MU/min.³⁴ Pardo *et al.* and Miri *et al.* investigated FFF beam dosimetry plans and found no clinically relevant deviations, but in these studies plans were not included using beams over ca. 1000 MU.^{35,36} Our test plans have high dose and high dose-rate values, that way the two small effects are summed and lead to increased deviations. Keeping the same optimization and using renormalization it was possible to evaluate the pure effect of the fraction size. According to our results the saturation effect can be clinical relevant using 6 MV-FFF energy with high dose-rate (1400 MU/min) and high fraction dose values, because it decreases the absolute CU values and the gamma passing rates. During the definition of action limits this effect has to be considered.³⁷⁻⁴⁰

Renormalization is a conservative, more rough diversion of the original, optimized plan, than changing prescribed isodose line. In that way any clinically relevant isodose level can be used for prescription, even a different fractionation scheme

can be safely applied without reoptimization. The change of the normalization after optimization keeps the DVH parameters, and the accuracy of dose delivery has no relevant diversion according to gamma passing rate results.

Hernandez *et al.* concluded that Varian machines prefer using MLCs or changing dose rates for dose modulation instead of gantry rotation speed.⁴¹ To describe the complexity of a treatment plan many types of metrics are used in radiotherapy.^{42,43} The ACM, which is applied for evaluation in this study, is related only to the MLC movement. According to our results the changed dose normalization does not change the MLC sequence, as can be concluded from Figure 2A. Meanwhile as Figure 2B shows, the used fraction dose during optimization has no effect on the ACM score. There is no consensus in the literature about the predictive usage of complexity metrics; for example, Park *et al.* have found correlation between metrics and gamma passing rates, but according to the study of Glenn *et al.* for a different metric there is no correlation.^{44–46} Based on our results, which can be seen in Figure 3, there is no clear connection between the complexity of the MLC pattern (ACM) and the gamma passing rates.

The changes (mean values and deviations) of gantry speed and dose rate or control point analysis can also be used to describe the modulation level of a treatment plan.⁴⁷ Huang *et al.* have made comparisons for cranial irradiation plans, focused on the changing dose rate and MU values and they found that plans with low daily dose, very high dose rate have to be handled carefully.⁴⁸ Our results show that the speed parameters of delivery do not predict the results of gamma analysis, as it is illustrated in Figure 4.

The strength of our study was the systematic and comprehensive analysis of the effect of different fraction dose values. The limitation of our results is caused by using only one measurement system (Portal Dosimetry), but this way it was possible to reach excellent spatial resolution and eliminate the additional errors from the usage of different measurement systems. Further investigation can be applied for in-vivo measurements and other beam energies.^{49–52}

The fraction dose used for optimization and the quality of the plan are independent from each other. Varying the prescribed isodose line can be applied safely, the delivery accuracy of the treatment plan is constant, moreover, the fraction dose can be changed after the dose optimization. Plan delivery parameters such as ACM, gantry speed and

dose rate changes do not predict the gamma passing rate values. According to the EPID-based dose measurements the gamma passing rate decreases in the case of high fraction dose and high dose-rate beams. This effect is caused by the saturation of the MV detector panel which has to be considered when the action limits of quality assurance system are defined.

Acknowledgments

This study was supported by the Hungarian Thematic Excellence Program of the Hungarian National Research Development and Innovation Office under grant Nr. TKP2020-NKA-26.

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