



Comparison of pre-treatment and in-vivo dosimetry for advanced radiotherapy of prostate cancer

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ABSTRACT

Background: The usage of advanced radiotherapy techniques requires validation of a previously calculated dose with the precise delivery with a linear accelerator. This study aimed to review and evaluate new verification methods of dose distribution. Moreover, our purpose was to define an internal protocol of acceptance for in-vivo measurements of dose distribution.

Materials and methods: This study included 43 treatment plans of prostate cancer calculated using the Monte Carlo algorithm. All plans were delivered using the Volumetric Modulated Arc Therapy (VMAT) technique of advanced radiotherapy by the linear accelerator Elekta VersaHD. The dose distribution was verified using: MatriXX, iViewDose, and in-vivo measurements. The verification also included recalculation of fluence maps of quality assurance plans in another independent algorithm.

Results: The acceptance criterion of 95% points of dose in agreement was found for pre-treatment verification using MatriXX; the average γ value was 99.09 ± 0.93 (SD) and 99.64 ± 0.35 (SD) for recalculation in the Collapse Cone algorithm. Moreover, using the second algorithm in the verification process showed a positive correlation $\rho = 0.58$, $p < 0.001$. However, verification using iViewDose in a phantom and in-vivo did not meet this γ -pass rate.

Conclusions: Evaluation of gamma values for in-vivo measurements utilizing iViewDose software was helpful to establish an internal dosimetry protocol for prostate cancer treatments. We assumed value at a minimum of 50% points of the dose in agreement with the 3%/3 mm criterion as an acceptable compliance level. The recalculated dose distribution of QA plans in regard to the Collapse Cone algorithm in the other treatment planning system can be used as a pre-treatment verification method used by a medical physicist in their daily work. The effectiveness of use in iViewDose software, as a pre-treatment tool, is still debatable, unlike the MatriXX device.

Key words: dosimetry; prostate cancer; quality assurance; in-vivo dosimetry

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Introduction

Prostate cancer radiotherapy

According to the World Health Organization (WHO), prostate cancer is the second most common type of cancer found in men [1]. During carcinoma, the overall size of the tumor increases,

and it is likely to invade the seminal vesicles with periprostatic tissues; however, the bladder and rectum wall can be invaded as well. Radiotherapy, radical prostatectomy, and internal radiation therapy (brachytherapy) are the three recommended types of treatments designated for prostate cancers. For radiotherapy, the total prescribed dose of treatment

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and the amount of dose per fraction depend on the severity of the regions involved [2]. Conventional radiotherapy is suggested when a locally confirmed tumor is limited only to the prostate gland; therefore, the total prescribed dose in our Radiotherapy Department is 74 Gy in 37 fractions (2 Gy per fraction) [3]. Another approach, the hypofractionated high dose intensity modulated radiotherapy (60 Gy, 20 fractions per 3 Gy), is equally successful and has been implemented recently. The main goal of the hypofractionation of prostate radiotherapy is to abbreviate unsolicited breaks between fractions, which might provide a better radiobiological effect for the overall effectiveness of treatment [4]. Recent studies have also shown that after hypofractionation of dose, the overall bowel and urinary condition, as well as sexual dysfunctions, are not significantly worse than conventional radiotherapy; therefore, the effects of hypofractionated radiotherapy have been studied recently [5].

Dynamic advanced radiotherapy technique

Over the years, a vast growth and development have been observed in advanced radiotherapy techniques. We can distinguish the 2-D radiotherapy technique, which is one of the oldest and rarely used nowadays and usually utilized for palliative treatment; 3D-CRT static fields and dynamic advanced techniques used worldwide [2]. The vast breakthrough occurred when the 3D-CRT technique came up allowing dose to be calculated in previously contoured structures in a three-dimensional space. This technique uses wedges to dilute or intensify a dose in a specific spot for the CT-scan of a patient's body [3].

Advanced radiotherapy techniques include, among others: intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and highly specialized stereotactic body radiotherapy (SBRT). These techniques exploit an accurate field's shaper, a multi-leaf collimator (MLC), embedded in the head of the accelerator gantry. The MLC blocks some of the unwanted radiation, especially directed towards sensitive and healthy tissues, with a high intent on reducing the dose outside the tumor area [6]. The IMRT radiation technique allows treating patients using several different modes, such as Sliding window or Step and Shoot [7]. In VMAT, a linear accelerator can radiate

while moving around the patient's body with the simultaneous movement of the MLC. These leaves are constantly forming a change in the radiation field. It allows a much more conformal treatment plan to be achieved with a high dose deposited into the tumor. Moreover, it provides one of the highest and effective coverage of the target [4, 8, 9]. Despite using advanced treatment techniques and dose calculation algorithms, it is still necessary for us to verify the appropriate position of the patient's body [10]. In our Radiotherapy Department, the patient's alignment is corrected by an applied imaging system named image guided radiation therapy (IGRT) [11].

Calculation algorithms in treatment planning system

The main purpose of radiotherapy is to deliver a previously prescribed dose straight to the tumor. Although a high dose is much awaited in the target (cancer), the other organs at risk need the lowest one [12]. A golden principle called as low as reasonably achievable (ALARA) is the most significant concept to optimize the planning process as much as to achieve a compromise between covering the target with the prescribed dose and separating other healthy tissues from unwanted radiation [4, 13, 14]. Regarding the differences in tissue density (homogeneous or inhomogeneous), the algorithm in the treatment planning system (TPS) has to consider diverse scattering through the tissue during the dose calculation process. Among these algorithms, we can highlight the Monte Carlo (MC) algorithm used in the Monaco treatment planning system delivered by the Elekta company. It is deemed as the gold standard in an advanced dose calculation process in radiotherapy and performs the statistical simulation of every single particle in a human tissue despite their differences [12, 15]. In Our Radiotherapy Department, the MC algorithm is held as a standard in the treatment planning process. Another calculating algorithm is the Collapse Cone (CC), which is applied in the second treatment planning system — RayStation. It is characterized as an analytical, non-statistical simulation approach [12]. The indicated dose calculation procedure takes into consideration particles which transfer and their scattering effects; thus the CC algorithm is also recommended for estimating the dose distribution in inhomogeneous tissues [15].

Dose detectors

There is a wide interest in developing accurate dosimetry tools, such as diverse detectors capable of reconstructing dose distribution in dynamic treatment plans [16–18]. For example, Delta4 phantom applies a 3D phantom with an array of diode detectors on two orthogonal planes. Octavius is a cylindrical phantom made of water-equivalent white polystyrene. According to its shape, the 3D dose distribution can be reconstructed by using a proper software [19, 20]. ArcCHECK is a cylindrical phantom made by a water-equivalent material: acrylic has 1386 diode detectors arranged in a 3D helical shape [21–24]. MatriXX is a two-dimensional (2D) universal detector array equipped with 1020 ion chambers with a total width of 32x32 grid used for dose measurements [18, 24]. During radiation, photons generate some secondary particles mostly via the Compton Effect process (the most common effect in this range of energy used in clinical treatment in radiotherapy). An acquired electrical charge in the ionization chambers after radiation (proportional to the dose rate) was compared with a previously prepared QA plan using IBA MatriXX software [25]. This dose verification method is used as a standard in the Radiotherapy Department at the Oncology Center in Opole. The biggest disadvantage of this method is that it must be done before the patient starts the treatment cycle. Since it is a charge analysis in a detector array equipped with ion chambers, measurements using that method must take place in a phantom. It has to be appropriately shaped for this detector; they cannot be performed in real time in the patient's body or using computed tomography of the patient's body. Another software, iViewDose, which uses iViewGT (Electronic Portal Imaging Device delivered by Elekta) is a new tool used for verification. The EPID panel acquires every image coming from each single arc of a linear accelerator, thus iViewDose software converts the detected signal to an absolute dose value in the reconstruction plane derived from computed tomography (CT) data of the phantom or patients after the image capture procedure. Then, using the 3D gamma analysis approach, the reconstructed dosage distribution is compared to the calculated dose distribution. Thus, iViewDose software is capable of summing up all acquired images up to create a 3D dose distribution in a phantom (pre-treatment measurements)

or in the patient's body (in-vivo). Furthermore, the possibility of using iViewDose for in-vivo measurements is very promising. The ability to verify the fluency of dose in real time would allow the patient to start radiotherapy earlier as well as to check the dose distribution daily. [26–29].

Gamma factor

The quality assurance protocols need to be enhanced by medical physicists in their daily routine [2]. One of the mainstream parameters for the evaluation of dose accuracy is the gamma factor. It is used to analyze if the difference between calculated (in TPS) and measured dose is acceptable as an assumption in a certain point of the treatment plan. Compliance with these criteria is achieved if gamma indices are below unity: $\gamma < 1$. The dose difference between measured and calculated points of the dose appears due to an inaccurate phantom or patient's positioning but also in the treatment plan itself — in steep dose gradients areas. Thus, the stricter and closer criteria for the points of dose (i.e., 2%, 2 mm and 1%, 1 mm), the fewer points of measured dose which are consistent with the previously calculated ones in TPS. The standard in radiotherapy is to meet a minimum of 95% of points in compliance with a minimum of 3% of dose difference within 3mm of the considered region. Some studies showed that a criterion of 2% in 2mm can show the compliance, however 1% and 1mm did not meet the assumptions of minimum 95% of points for prostate cancer cases. We conducted our measurements regarding our internal protocol, according to international reports, our criterion in 3%/3mm of dose difference in the maximum distance was determined [23, 24, 30–32].

This study had several objectives: 1) to investigate and compare various dosage verification methods used in radiotherapy, such as quality assurance utilizing MatriXX and EPID devices, 2) to recalculate fluence maps using the second, more varied TPS, and 3) to acquire in-vivo measurements to assess dosage compatibility during the patients' treatments.

Materials and methods

Clinical sample

The clinical sample consisted of 43 male patients ($M = 72.28$ years, $SD = 5.95$) diagnosed with pros-

tate cancer. Individuals were then examined by Computed Tomography (CT) in a supine position with immobilization (vacuum bag) applied under the legs. All the patients followed the same protocol before CT-examination (i.e., filled bladder and empty rectum) in every fraction of daily radiotherapy. For each patient, VMAT plans were optimized by the Monte Carlo algorithm in Monaco (version 5.11.02) using 6MV photon beam energy in two single 365-angle arcs. The radiation was delivered by the linear accelerator Elekta VersaHD, equipped with the MLC (Agility: 5 mm leaf width).

Methods of verification

According to the dosimetry protocols, quality assurance plans (QA) are required and need to be prepared before starting a treatment. In this survey, four types of dose verification have been accomplished. In each of them, the gamma factor has been used to show significant differences between calculations in the treatment planning system and measured dose distribution. The fluency of the dose from the TPS was computed using Monte Carlo algorithm (Monaco TPS) and verified in 2D utilizing a MatriXX detector (1). The second independent method of pre-verification has been accomplished using iViewDose (2). The third method consisted of measuring the dose distribution in the patient's body during a real treatment in vivo (3). The acquired dose was scattered by patient's body and then compared to the dose distribution calculated in iViewDose software. Furthermore, each of the 43 prostate treatment plans were transferred to RayStation TPS (RaySearch Laboratories), then the dose calculations established the same beam settings as in Monaco TPS (Elekta), but the algorithm was modified into the Collapse Cone. Thereafter, the two fluence maps of quality assurance plans (rooted in MC and CC algorithm) were compared in the IBA MatriXX software using the gamma factor [4].

Statistical analysis

First, due to the non-normality of the data, Spearman correlation and its 95% confidence interval (CI) were estimated to assess the relationship between the study variables. P-values were computed via the asymptotic *t* approximation. Lastly, in order to compare the accuracy and precision between the calculated and measured points of dose, first (MatriXX) and second (iViewDose) method, a Wil-

coxon rank-sum with continuity correction, was performed. All statistical analyses were performed in R 4.0.2. The significance level was set at 0.05.

Compliance with ethical standards

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Ethical approval was not necessary for the preparation of this article.

Results

The dose distributions from 43 treatment plans were calculated, measured, reconstructed by using the two different acquisition methods (ion chambers — MatriXX and EPID device) and recalculated in the second independent algorithm which is the Collapse Cone. Additionally, the in-vivo measurements during each treatment session were done for every patient (in-vivo). For the purpose of our analysis, we calculated the average value of gamma passing rate from each fraction, SD and median which are presented in Table 1. The gamma passing rate was used to analyze the conformity between them (see Table 1 for a summary of the data). The treatment plan is accepted and approved when more than 95% of the measured points of dose are comparable to the calculated ones within a global gamma index which is lower than 1. The agreement criterion was: 3% dose difference and 3 mm distance between points [25]. All performed measurements using the MatriXX device met the acceptance criterion, which consisted of more than 95% of the evaluated points of dose in agreement. In contrast, this criterion has not been reached for the second and third verification method utilizing the iViewDose software and EPID for all the cases.

Results displayed a non-significant association between the first two methods (1) and (2) of measurements, $\rho = -0.03$. When comparing a verification technique that reconstructs dose distribution in two-dimensional space (2D) to a three-dimensional one (3D), significant differences are expected. The Wilcoxon Signed-Ranks test indicated that gamma values measured via the MatriXX detector were higher ($Md = 99.52$) than those measured by the iViewDose detector ($Md = 95.67$), $W = 532$, $p < .001$. The correlation between the two 3D verification methods (2) and (3) showed that there

Table 1. Descriptive statistics of gamma index passing criteria ($\gamma < 1\%$) for each algorithm

	1 (MatriXX)	2 (iViewDose)	3 (in-vivo)	4 (MatriXX MC-CC)
Valid	43	43	43	43
Missing	0	0	0	0
Mean	99.09	90.59	83.24	99.64
SD	0.93	10.27	13.29	0.35
IQR	0.76	16	21.12	0.28
Minimum	96.05	58.51	51.55	98.63
Maximum	99.99	100	99.99	99.96
50th percentile	99.52	95.67	82.76	99.75

SD — standard deviation; IQR — interquartile range

was a non-significant association between the two points of dose ($\rho = 0.03$). Despite the fact that these two methods reconstructed the dose distribution in three-dimensional space (3D), they are different and must not be used interchangeably. In addition, the average gamma values measured in miniPhantom and reconstructed by iViewDose were higher ($Md = 95.67$) than those measured in a patient during in-vivo measurement ($Md = 82.76$), $W = 1292$, $p < .001$. Regarding the in-vivo measurements (3), the results showed lower points in agreement (gamma mean value: 83.24) compared with the iViewDose: 90.59. These gamma values were also the lowest compared with the other used methods. Table 2 summarizes the Spearman's correlations among these methods of verification, calculations, and in-vivo.

The fourth part of this study includes a comparison of fluence maps of dose distributions from the

basic, originally applied Monaco TPS (based on the Monte Carlo algorithm) and recalculated in a second, different one: Collapse Cone (CC). As shown in Table 1, it can be observed with a high gamma mean value ($M = 99.64\%$; tolerance of 3%/3mm for the dose difference and distance to agreement). The correlation coefficient between the local points of dose calculated using the MC algorithm in Monaco TPS and CC algorithm in RayStation TPS showed a positive association between two points of dose, $\rho = 0.58$, $p < .001$. Figure 1 summarizes the relationships between these diverse dose verification methods.

Discussion

The results from this study suggest that each treatment plan must be compulsorily verified before launching it into the treatment process. These

Table 2. Spearman's Correlations among these methods of verifications, calculations, and in-vivo

Variable		1 (MatriXX)	2 (iViewDose)	3 (in-vivo)	4 (MatriXX MC-CC)
1 (MatriXX)	Spearman's ρ	–			
	Upper 95% CI	–			
	Lower 95% CI	–			
2 (iViewDose)	Spearman's ρ	–0.027	–		
	Upper 95% CI	0.276	–		
	Lower 95% CI	–0.325	–		
3 (in-vivo)	Spearman's ρ	0.473**	0.029	–	
	Upper 95% CI	0.677	0.327	–	
	Lower 95% CI	0.201	–0.274	–	
4 (MatriXX MC-CC)	Spearman's ρ	0.580***	0.038	0.312*	–
	Upper 95% CI	0.750	0.335	0.560	–
	Lower 95% CI	0.339	–0.265	0.013	–

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. CI — confidence interval

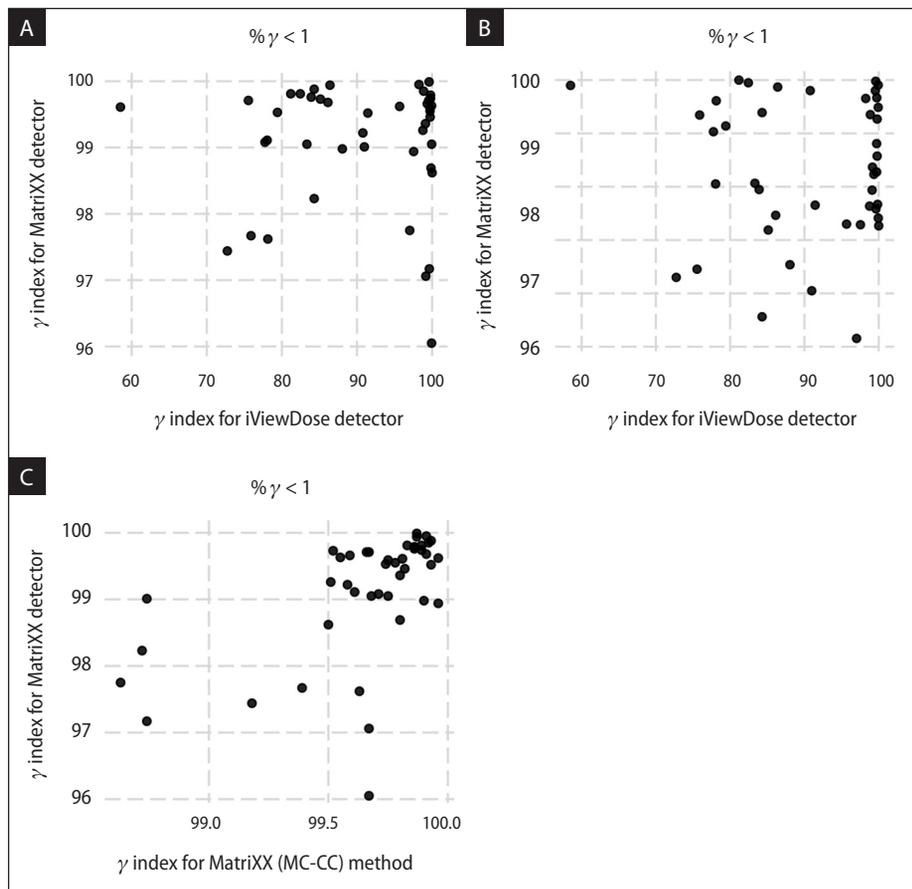


Figure 1. The relation between gamma index values verified by: 1-MatriXX and 2-iViewDose (A), 2-iViewDose and 3-in-vivo (B), 1-MatriXX (MC) and 4-miniMatriXX (MC-CC) (C)

actions are carried out by utilizing a suitable device; for example, the MatriXX detector delivered by IBA Dosimetry. These actions are aimed to ensure that the dose distribution calculated and defined in a treatment planning system (TPS) is included and delivered in a certain range of tolerance (3%/3 mm) [11]. The most straightforward method to compare the two dose distributions is using the gamma value factor [28]. The aim of this research was twofold. First, we aimed to study and make a comprehensive analysis between the different dose verification methods applied in radiotherapy such as IMRT QA. Using MatriXX and EPID devices or recalculating using the second, diverse TPS. Secondly, we evaluated the dose compatibility in the course of the patient’s irradiation: in-vivo measurements.

Pre-treatment verifications of dose distribution using MatriXX and EPID

The quality and reliability assessment of measured and calculated points, in our Radiotherapy

Department, was established on the gamma factor and 95% of points in the agreement. The values and distance of these points of dose, which create dose distribution, were obliged to be less than 3mm/3% of the dose difference. All the patients who participated in the study reported passing a criterion of acceptance using the MatriXX device as a pre-treatment verification measurement; nevertheless, data received from iViewDose did not achieve our passing level. It is worth mentioning that the measurement performed using the MatriXX detector receives scattering from the air and a phantom with a treatment couch. On the other hand, scattering applying the EPID contains air, phantom, treatment couch, air, and the EPID panel with detectors. Some of the other inconsistencies during measuring when using the MatriXX might have occurred. Especially when the plan’s geometry contains lots of radiation from sideways of gantry angles. Therefore, the limitation of measurement appears when a plane of the detector array is not perpendicular

to the source of radiation. Concluding, verification measurements must not be done alternatively when in conjunction with the MatriXX and iViewDose, as a pre-treatment dose distribution assessment. By comparing these two methods, we primarily wanted to test the measuring performance of the new iViewDose software in comparison to the already well-known MatriXX detector. Both methods involve the use of a phantom and reconstruct the dose in two planes and can be used to verify dose fluence before the patient starts radiotherapy. As a visible weakness they still do not provide real-time information about the dose distribution in the patient's body during the treatment. In our opinion, the usage of the iViewDose software might need to establish less than 95% of points in the agreement of the gamma factor; nevertheless, each action leading to a decrease in the criterion of acceptance in quality assurance must be treated carefully. However, the main strength of using the iViewDose is utilizing a similar transfer, algorithm, and processing of the acquired data to future in-vivo measurements.

Different dose calculation algorithms

To be capable of estimating dose distributions in various tissues and structures, the whole treatment process uses a CT-scan examination. Interestingly, the results of this study indicated excellent dosimetry compatibility and consistency between the Monte Carlo and the Collapse Cone algorithm even when both methods were using different scattering estimates in homogeneous and inhomogeneous tissues, results were significantly similar. Recalculating the dose fluency in the second independent calculating algorithm and treatment planning system is undeniably the fastest verification that can be performed before a patient begins radiotherapy. Thus, these two treatment planning systems – Monaco and RayStation — can be applied alternatively as a pretreatment verification tool for comparison fluence maps of quality assurance plans. However, this type of verification does not detect any errors or geometrical difficulties related to radiation delivery by the linear accelerator.

In-vivo verification of dose distribution using iViewDose software

Some studies presented slightly higher gamma values of the in-vivo data comparing to a pre-treatment verification measurement. However, this

strong correlation has been achieved for IMRT treatment plans [27]. In the course of the dose calculation process, in the treatment planning system, it is still unknown how the dose will be deposited in the patient's body with every fraction. These uncertainties contain the patient positioning, preparation, and some of the linear accelerator's features (i.e., the difference in the daily dose rate mode). All of these factors may have a significant effect on a real dose delivered to the patient; therefore, the in-vivo measurements would be helpful. The iViewDose dosimetry system has a prevalence in measuring how the dose distribution changes and might also predict some possible modifications in the patient's anatomy in every fraction of radiotherapy. It relies on some conditions; for example, the tumor "melting" after radiation when the shape and extent might change. On the other hand, some healthy tissues might start to swell up or shrink as a biological response to radiation (radiobiological effects). So far, we have only verified the group of patients with prostate cancer utilizing the iViewDose technique. The average value of the gamma factor for this method was 83.24%, but based on our study, the acceptance level for pre-treatment measurements of all clinical samples passed our criterion using the MatriXX. Thus, we created our internal criterion of acceptance for in-vivo at 50% points compliance based on our 3 mm/3% tolerance criterion (minimum value for the in-vivo method was 51.55%, maximum 99.99% and average 83.24%; all the data is summarized in Table 1). In order to establish the general criterion, large amount of in-vivo measurements is required, and the other regions should be investigated too. We need to be aware that these results of in-vivo measurements might have been much lower due to the specifications of the treated region. Daily changes in filling of the bladder and emptying the rectum play an enormous role in effective dose deposit in treating prostate patients. These factors are also in place for cervix or bladder cancer patients. In order to broaden the scope of this topic, it is required to conduct the in-vivo measurements for other cancer regions. It is also advisable to perform these measurements on another anthropomorphic phantom. Nevertheless, major advantages come from measuring the fluence of dose in real-time and are worth looking into further. Besides the dose, these measurements might also detect some errors and

geometrical limitations which cannot be predicted without patients lying on the treatment table at an isocentric distance from the gantry of the accelerator linac.

Summing up, the main advantage in having different methods of dose verification is that they can be chosen alternatively depending on the current need. Using MatriXX and EPID can be helpful to find major errors in delivering the 2D dose to the phantom. Also, recalculating the dose fluency, using the other calculating algorithm, as a quality assurance procedure can verify the major mistakes of prepared plans. Lastly, iViewDose, as in-vivo software, can provide new different information daily after real-time measurement in the patient's body. Moreover, this method can detect some treatment's plan geometrical limitations which cannot be checked previously without the patient.

Nevertheless, the main disadvantage of using 2D measuring methods is that it does not provide data of the patient's treatment in real time or his daily preparation. On the one hand, implementing in-vivo 3D measurements can present current changes of the dose; however, it needs implementing new levels of gamma factor's acceptance for each treated region. On the other hand, as presented in this study, medical physicists must consider whether the low gamma factor, after in-vivo measurements, indicates errors or is just related to the treated region and chosen method of dose verification.

Conclusions

Pre-treatment verification methods are routinely used in radiotherapy departments; however, in-vivo dosimetry of the dose is a promising and future-proof method. Gamma analysis has been considered as an effective dose distribution evaluation tool and provided satisfactory results. Comparison of different methods of pretreatment dosimetry and in-vivo has been found to be very suitable for determining an internal criterion of acceptance for the in-vivo method at 50% points compliance based on 3mm/3% tolerance gamma criterion. Recalculating fluency of dose in the second independent treatment planning system is also helpful to present any differences in dose without using radiation.

Conflict of interests

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