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Research article

In vivo dosimetry for patients with prostate cancer to assess possible impact of bladder and rectum preparation

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ABSTRACT

Purpose/objective: In all treatment sites of our radiotherapy network, in vivo dosimetry (PerFRACTION™) was fully implemented in February 2018. We hypothesized that additional help with bladder and rectum preparation by home nursing would improve patients' preparation and investigated if this could be assessed using in vivo dosimetry (IVD).

Materials/methods: A retrospective study was conducted with a test group who received additional help with bladder and rectum preparation by home nurses and a control group who only received information on bladder and rectum preparation according to the standard protocol. Patients were treated with a 6 MV Volumetric Modulated Arc Therapy (VMAT) technique. Electronic portal imaging device (EPID)-based integrated transit dose images were acquired on the first 3 days of treatment and weekly thereafter or more if failed fractions (FF) occurred. Results were analyzed using a global gamma analysis with a threshold of 20%, tolerance of 5% (dose difference) and 5 mm (distance to agreement), and a passing level of 95%.

Results: Data of 462 prostate patients was analyzed: 39 and 423 in a test and control group respectively with a comparable number of measurements (on average 8.0 (σ = 4.8) and 7.1 (σ = 4.5) respectively per treatment course). Of the FF, 39% and 31% were related to variations in bladder and rectum filling for the test and control group respectively. Subgroups were created based on the number of FF, no statistically significant differences were observed.

Conclusion: Two dimensional EPID-based IVD successfully detected deviations due to variations in bladder and rectum filling, however it could not confirm the hypothesis.

Introduction

It is recommended by both the International Atomic Energy Agency (IAEA) and the European Society for Radiotherapy and Oncology (ESTRO) that in vivo dosimetry (IVD) be used in standard practice of radiotherapy (RT) departments [1,2,3].

A recent review of an incident database reported that IVD performed during the first fraction of treatment has the potential to detect the majority of clinically reported incidents [4]. With the introduction of Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), IVD using point dosimeters became challenging and other approaches have been explored. Electronic Portal Imaging Devices (EPIDs) offer the possibility to verify the dose distribution in 2D/3D during the treatment and no additional time is needed for pretreatment imaging [5]. It has been shown that IVD using EPIDs for transmission dose measurements is a reliable patient-specific quality control tool to detect deviations [5] and has been introduced in many centres as routine practice [6,7]. Several studies have evaluated the sensitivity of EPID-based IVD for relevant clinical deviations, which depends on the methods and gamma criteria used [8,9]. The relative performance of these methods in identifying specific types of deviations is still challenging. Bojechko et al. reported that EPID-based 2D IVD can detect small variations in dose and systematic shifts of the MLC's, but changes in patient's habitus and shifts in the patient's position were more difficult to detect [4]. Bedford et al. showed that the EPID-based 2D and 3D IVD for prostate patients were not able to identify possible source of errors related to spatial shifts or bowel gas [10]. An automated EPID-based software platform (PerFRACTION™, part of SunCHECK™, Sun Nuclear

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Corporation) was introduced for patient-specific QA and IVD of all patients in our department [11] to detect major deviations and assess clinically relevant differences between planned and delivered dose. In this report a cohort of patients with prostate cancer was evaluated in more detail. A recent study by Olch et al. showed that this approach has the potential to identify changes in patient anatomy, patient setup and beam delivery [12].

For the treatment of prostate cancer, several studies already emphasized that a full bladder and empty rectum during the RT planning scan and daily treatment are recommended [13,14,15]. Tsang et al., recently, stressed the importance of using an empty bladder/rectum preparation protocol, which has been shown to be clinically relevant and can provide better patient comfort and reproducibility [16]. However, this protocol is not used in our department. Yaver et al. indicated that bladder and rectum preparation can influence the geometries and volume of both organs and affect dose exposures and toxicities [17], and others indicated possible dosimetric variations affecting normal tissue complication probability [18,19,20]. The introduction of image guidance techniques using kilovoltage (kV/kV) and gold fiducial markers or kilovoltage cone-beam computed tomography (kV-CBCT) imaging has brought about a reduction in toxicity [21] and help in finding out the daily variation in bladder and rectum volume due to variable filling during the course of treatment [22]. In our study, 2 groups of prostate cancer patients have been observed: 1) a control group receiving information on bladder and rectum filling the conventional way during the intake consultation (prior to simulation), and 2) a test group that was monitored and followed by home nurses (White Yellow Cross, Belgium). The aim of the current study was to capture and evaluate the effects of bladder and rectum preparation in routine RT treatment for prostate cancer on IVD. We hypothesized that help with bladder and rectum preparation by nurses would improve patients' preparation and investigated if this could be assessed using IVD.

Materials and methods

This study was approved by the "Stuurgroep Iridium" in October 2018, aiming to involve a maximum of 40 patients (test group) with prostate cancer living in Antwerp who can be assisted by home nurses for a full bladder and empty rectum protocol. All prostate cancer patients enrolled had given their written informed consent. Patients with primary prostate cancer were treated with a hypofractionated schedule (20 fractions of 3.0 Gy or 25 fractions of 2.64 Gy) if they had localized, intermediate-risk disease or with conventionally fractionated schedule (35 fractions of 2.2 Gy) if they harbored high-risk or locally-advanced disease. In the post-operative setting, all patients received 35 fractions of 2.0 Gy. A script was created to retrieve the 2D analysis results of the IVD from the database. The retrospective assessment was performed by evaluating comments related to the failed fractions (FFs) from both medical physicists (MPs) and radiation oncologists (ROs) in the software application and patient file.

All treatments were planned on Eclipse (v13.6, Varian Medical Systems, Palo Alto, CA, USA), using the Analytical Anisotropic Algorithm (AAA, v13.6.23) dose calculation model and delivered on Varian TrueBeam and Clinac-iX systems, using 6 MV photon beams with VMAT technique. Each treatment fraction was delivered by a two-arc plan consisting of a clockwise (CW) and counterclockwise (CCW) gantry rotation.

During the initial RT consultation, the ROs explained the bladder and rectum preparation protocol to both groups; a written summary of the protocol was provided for all patients. Patients were instructed to start drinking fluids regularly throughout the day, and maintain an intake of at least 1.5L of water per day to ensure that they were well hydrated. Patients' compliance with the hydration protocol, dietary and urinary adverse events were recorded for every fraction in the patient file. On the day of the simulation appointment, patients of both groups were instructed to empty their bladder and bowels (using Microlax) 1 hour prior to CT and MRI simulation and were then instructed to drink two cups of water (maximum 400 ml). The same scenario was repeated for each treatment fraction, but for rectum preparation, glycerin suppositories were used for treatment instead of Microlax because it gave less irritation. The test group received help from home nurses for this preparation during the whole treatment. The home nurses explored the individual's understanding of the preparation protocol, assisting them at every step of the preparation, including answering questions about existing symptoms and what to expect from the treatment.

During treatment, on-board kV-CBCT was used as routine check for every prostate cancer patient without fiducial markers to evaluate bladder and rectum filling status, and improve the geometric accuracy of target localization. For patients with fiducial markers, daily kV-kV imaging was performed. It needs mentioning that in case a large deviation in bladder or rectum filling was observed on the kV-CBCT prior to treatment, patients were instructed to re-initiate the preparation protocol before resuming treatment.

PerFRACTION™ version 2.2 was implemented on a dedicated server running with database software and a web interface for configuration and data analysis. After the treatment plan had been approved by MPs and ROs, the patient treatment plan information was pushed via Digital Imaging and Communications in Medicine (DICOM) export into the application, where it was automatically imported and processed. The linacs (TrueBeam and Clinac-iX) were equipped with aS1200 or aS1000 EPIDs flat panel detectors. During treatment delivery the MV panel deploys and collects an integrated image of each beam delivery. The images were automatically saved in Varian ARIA and imported by the software application for analysis using an automated query retrieval process.

For IVD, the acquisition was performed on the first 3 days of treatment and weekly thereafter (or more in the event of FFs). A forward-projection method is used to predict the EPID signal using the beam geometry and planned dose distribution that is expected to occur during a fraction of treatment. The calculated dose is projected to the plane of the EPID and the expected EPID signal is obtained applying an EPID panel response function [10,23]. The advantage of this method is that the predicted and measured images can be summed over all control points of the arc to give a single predicted and measured image respectively for comparison. Calibration fields calculated in a water phantom are mapped to generate a dose-per-signal conversion factor matrix for the panel. The EPID images are then processed through this dose conversion matrix into absolute dose.

Results were analyzed using a global gamma analysis with a threshold of 20%, a dose difference (DD) of 5%, a distance to agreement (DTA) of 5 mm and a passing level of 95%. These settings were the result of previous large scale evaluation to reduce the number of false positive (FP) results [11]. Irregularities were automatically detected and inspected by MPs to identify suspicious situations such as bladder and rectum filling that may have affected delivery. On the following day, the radiation therapy technologist (RTT) would be instructed to acquire kV-CBCT images for investigation to confirm the presumed cause of deviation.

For each treatment fraction, the results of gamma analysis were automatically generated (both per arc and per fraction), specifying if it passed or failed the criteria. The fraction analysis is based on the average value of passing tolerance level of all beams (i.e. the average value of all beams must be equal or greater than 95%). As a result, it can happen that a fraction passes with 1 failed and 1 passed beam. The results of QA and IVD can be easily accessed, managed and analyzed using structured query language (SQL).

All causes and actions undertaken were investigated, but only the failed results due to bladder and rectum/bowel filling will be

taken into account and/or discussed in this report. For each failed treatment fraction, only a single specific cause and action undertaken was assigned, avoiding double counting. If failure was due to more than one reason, the cause with the largest contribution to the failure was assigned.

The adherence to bladder and rectum filling according to the IVD assessment was evaluated in the control and test group. Prostate cancer patients in each group were classified into 3 subgroups according to the number of FFs. In group A patients had at most 1 FF, considering bladder and rectum/bowel filling to be stable. In group B patients had 2–4 FFs assuming bladder and rectum/bowel filling was less consistent. In group C patients had more than 4 FFs, meaning bladder and rectum/bowel filling fluctuated. Parametric *t*-test for two independent samples/two-tailed (using XLSTAT software) was carried out on the data where possible, including the evaluation of the mean value, standard deviation, and 95% confidential intervals.

Results

The data of 462 prostate cancer patients was extracted from the database: 39 of the test group and 423 of the control group. The amount of exit dose images taken per patient in both groups were comparable: 3305 fractions in total, 312 (9.4%) in the test group with mean value of 8 fractions measured per patient per treatment course (standard deviation, $\sigma = 4.8$) and 2993 (90.6%) in the control group with a mean of 7.1 fractions measured ($\sigma = 4.5$). The statistical analysis was performed under the hypothesis of equal mean. The mean of sample variance corresponding to the two groups was 4.5. Under normality, and a type I error probability of $\alpha = 0.05$, the *t*-test absolute value of 1.22 fell below the critical value 1.97 ($1 - \alpha/2$, p = 0.22). In addition, the 95% confidence limits for the mean difference ranged from −2.41 to 0.56. This interval contained 0, hence there were no statistically significant differences between the measured fractions in both groups. However, this could possibly be due to the study being underpowered ($\beta = 0.77$, power = 0.23 < 0.8). Only FFs that were attributed to bladder and rectum filling are discussed in this study. FFs related to bowel/rectum filling and bladder filling respectively were 16% and 15% in the control group compared to 22% and 17% in the test group. The most occurring action undertaken was the acquisition of a new IVD measurement and extra imaging to verify patient positioning. The recommendation for plan adjustments in the control and test group was 3% and 2% respectively, which was minor compared to the recommendation of repeating the measurement during the next fraction after a new bowel and rectum preparation, 8% and 19% for both groups respectively.

Classifying the 2 groups of patients in function of the number of failures, yields the following results: 1) in the control group, 93.1% of prostate cancer patients had at most 1 FF, considering bladder and rectum/bowel filling to be stable (group A) compared to 89.7% in the test group; 2) in the control group, 4.3% of prostate cancer patients had 2–4 FFs assuming bladder and rectum/bowel filling was less consistent (group B) compared to 5.1% in the test group; and 3) in the control group, 2.6% of prostate cancer patients had more than 4 FFs, meaning bladder and rectum/bowel filling fluctuated (group C) compared to 5.1% in the test group. These results are summarized in Fig. 1.

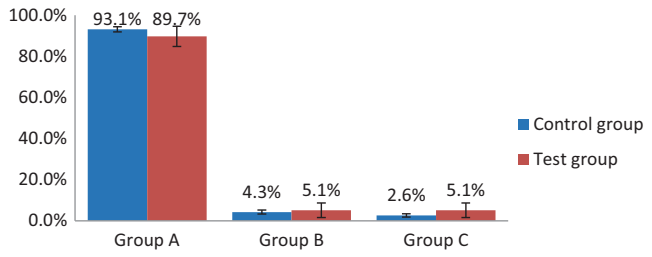

Fig. 1. The adherence to bladder and rectum filling for prostate cancer patients in the control and test group. Group A, patients who had at most 1 FF, considering bladder and rectum/bowel filling to be stable. Group B, patients who had 2–4 FFs assuming bladder and rectum/bowel filling was less consistent. Group C, patients who had more than 4 FFs, meaning bladder and rectum/bowel filling fluctuated.

Discussion

This study was designed to assess whether EPID-based IVD could be used to evaluate the effects of 2 different methods of patient preparation in bladder and rectum filling: self preparation (control group) and assistance received during the course of treatment (test group). The analysis was performed based on the comments of FFs made in the software application. The comments were carefully investigated to discover the reason for FFs as the dosimetric impact to the patient is not straightforward [10].

An automated EPID-based IVD depends on the sensitivity of the software application to detect clinical relevant deviations. Olch et al. previously reported that an automated EPID-based system can flag potential daily treatment deviations [24]. The software allows the user to choose the level of sensitivity for clinical use, based on the gamma index and passing rate. A generous choice of the latter could jeopardize the sensitivity of the software application increasing false negative (FN) results. The number of FP, on the other hand, increases as tolerance levels are tightened. At the experimental stage, our centre started with a 3% DD and 3 mm DTA (resulting in a too high failure rate) after which a more practical gamma index was introduced based on the PTV margin as distance tolerance level. A disadvantage of the forward-projection method is that the dose in the patient cannot be reconstructed and interpretation of the difference in predicted and measured EPID images is challenging. In this study, all patients with prostate cancer were analyzed with a global gamma index (5% DD/5mm DTA) and 95% passing rate which was considered clinically relevant in avoiding too many FNs [11].

Statistically, no significant differences were observed between both patient groups. Although clear instructions were given to prostate cancer patients regarding bladder and rectum preparation, the analysis indicated that there were variations in bladder and rectum filling, which caused 31% and 39% of FFs in the control and test group respectively. The variations in bladder and rectum filling were comparable in both groups. The standard method without additional help from home nurses was as effective in achieving consistency in bladder and rectum filling when we compare the results in this study.

A kV-CBCT or kV-kV imaging was acquired prior to dose delivery to correct patient setup issues and deformations due to air bubbles in the rectum. As reported by Olch et al [24], the latter could be identified as a major cause of significant variations in dose and these corrections should have mitigated the causes of FFs related to patient positioning and patients preparation. Some studies have reported that a bladder scanner (bladder ultrasound device) could be useful to assess the interfractional variation of bladder and rectum volume [24,25,26]. This also indicates that additional methods might be indicated in combination with standardized drinking and voiding methods.

In our study the adherence to bladder and rectum filling was comparable for both groups. The results have shown that 93.1% and 89.7% of prostate cancer patients had at most 1 FF, considering bladder and rectum/bowel filling to be stable (Group A) in the control and test group respectively. These results were considered acceptable for a busy centre because only 2.6% and 5.1% of prostate cancer patients had more than 4 FFs, meaning bladder and rectum/bowel filling fluctuated (group C) in the control and test group respectively.

As no statistically significant differences have been observed in the IVD data, we cannot confirm our initial hypothesis that IVD can verify whether monitoring and follow-up by home nurses improves prostate cancer patients' adherence to bladder and rectum filling. Possibly there is another interfering variable in that the RTT's pay attention to bladder and rectum filling prior to treatment based on the kV-CBCT or kV-kV imaging. As such, some patients who don't comply to the preparation conditions are filtered out.

The authors acknowledge that the small number of patients in the test group and unequal sample sizes introduce a limitation and bias to the study's results.

Conclusion

Two dimensional EPID-based IVD successfully detected bladder and rectum filling deviations when an appropriate gamma index and passing rate was implemented.

We hypothesized that personalized follow-up would improve patients' bladder and rectal preparation and therefore patient outcomes including greater precision. However, this was not confirmed by dosimetric analysis. The authors acknowledge two areas of possible bias; firstly this may be due to the large difference in the number of patients in both arms of this retrospective trial. Secondly it was not possible to implement controls, therefore it is possible that patients who did not initially comply with bladder and rectal preparation were discovered by RTT's on the kV-CBCT or kV-kV prior to dosimetric analysis. A future substantive trial should aim to reduce bias and to set controls to limit confounding factors.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors have an on-going scientific collaboration with Sun Nuclear Corporation.

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Appendix

See Table 1.

Table 1
Power analysis for two-group independent sample *t*-test based on equal mean.

Results	
Parameters	Results
Sample size 1	423
Sample size 2	39
alpha	0,05
Mean (Group 1)	7,07
Mean (Group 2)	8
Std. deviation (Group 1)	4,487
Std. deviation (Group 2)	4,84
Beta	**0,767**
Power	**0,233**

Test interpretation:
H0: The difference between the means is equal to 0.
Ha: The difference between the means is different from 0.
The risk to not reject the null hypothesis H0 while it is false is 0,767.
For the given parameters, for an alpha of 0,05 and a sample size of 423 observations, the type 2 error is 0,767 and the power is 0,233.

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