Frontiers in Biomedical Technologies Vol. 11, No. 1 (Winter 2024) 48-58

ORIGINAL ARTICLE

Dosimetry Impact of Bladder Volume Changes and Rectum Filling/Emptying at Proton Therapy of Prostate Cancer: A Simulation Study

Abedin Paydar, Ahmad Esmaili Torshabi *

Department of Nuclear Engineering, Faculty of Sciences and Modern Technologies, Graduate University of Advanced Technology, Kerman, Iran

*Corresponding Authors: Ahmad Esmaili Torshabi
Email: ahmad4958@gmail.com

Received: 05 September 2022 / Accepted: 20 November 2022

Abstract

Purpose: In the recent decade, proton therapy facilities are increasing worldwide. This study aimed to analyze the influence of volumetric changes in bladder and rectum filling on the dose received by normal surrounding tissues at prostate cancer proton therapy. In this work, an anthropomorphic phantom dedicated to the prostate organs and nearby tissues has been developed using the FLUKA simulation code.

Materials and Methods: The geometry of the prostate and normal nearby tissues, bladder volumetric changes, and rectum filling/emptying status were simulated according to a database of real patients to mimic actual treatment, assuming the prostate as the target receives the prescribed dose uniformly with no over- and under dosage at each treatment session. Furthermore, the dosimetric effect of air- and water-filled balloons as prostate fixation tools was considered on the rectum, during our simulation process.

Results: Final analyzed results showed that the overall dose received by normal nearby organs with be decreased at proton therapy of prostate cancer if the bladder is full, although this dose reduction is not remarkable. Moreover, rectum filling/emptying and also implementation of balloons with different matters have no significant effect on the amount of dose received by this organ.

Conclusion: The dosimetric impact of bladder volumetric variations onto normal nearby organs will not be a crucial issue in proton therapy of prostate cancer if the prescribed high dose is delivered on the target with proper uniformity laterally and in-depth. Based on the obtained results, a full bladder is recommended while target bombarding by a proton beam.

Keywords: Prostate Cancer; Proton Beam Therapy; Bladder; Rectum; Balloon.

DOI: https://doi.org/10.18502/fbt.v11i1.14511

1. Introduction

Prostate Cancer (PC) is known as one of the most common cancers among men [1]. The lifetime risk of developing PC is 1 in 8, and it is expected that the incidence will substantially increase in the coming decades due to the aging population, which makes it a big healthcare issue [2, 3]. Several efforts have been proposed as prostate curative treatment options, most commonly as surgery, chemotherapy, or radiotherapy [4, 5]. The latter modality plays an important role while a large number of patients with prostate cancer have undergone clinical external-beam radiotherapy or brachytherapy in recent decades. Permanent prostate brachytherapy known as the Low Dose Rate (LDR) strategy is performed by permanent implanting of multiple radioactive seeds inside prostate tumor volume by means of a real-time trans-rectal ultrasonography monitoring system [6]. At external-beam radiotherapy, a very careful delivery of the prescribed dose onto the prostate tumor will significantly enhance treatment quality while the surrounding healthy organs are affected as little as possible, at the same time. In conventional radiotherapy, patients need to be irradiated in pre-defined fractionated courses, during the whole treatment time extending for two months or more in some cases [6]. At each irradiation fraction, patient geometrical setup is required to align tumor volume in front of the therapeutic beam, to minimize intra- and inter-fraction motion errors. The latter error represents an anatomical change of the patient body in between the treatment fractions [7].

In clinical routine, the concept of patient positioning and tumor alignment will be a crucial issue for medical physicists in external radiotherapy to yield better dose conformity onto tumor volume [8]. This concern raises significantly for patients with prostate cancer due to the tumor site in the thorax region and its non-rigid type.

At prostate cancer radiotherapy, apart from intra-fractional motion error [9], the prostate is highly influenced by anatomical and volumetric changes in the bladder and rectum as nearby adjacent organs, at each irradiation fraction. These changes are not negligible and can lead to over and/or under dosage of prostate tumor volume [10-13]. Furthermore, normal nearby tissues such as the rectum as an Organ at Risk (OAR) may receive a high dose, and the risk of toxicity is increased, accordingly [14]. Several efforts have been done to address this issue.

In 2007, Vitaly Moyzenko *et al.* investigated the effect of bladder filling on the prostate nearby organ at risk doses in the framework of treatment planning. In the mentioned study, while the bladder is full and empty, the mean effective doses received by the rectum as OAR are 55.6 Gy and 56.8 Gy, respectively. Moreover, while the bladder is full and empty, the effective doses received by the bladder organ are 29 Gy and 49.3 Gy, respectively. In 6 patients with prostate cancer, a part of the small intestine with 2.5-30 cm^3 volume has received more than 50 Gy with empty bladders. It should be noted that bladder filling did not have a significant effect on the uniform equivalent dose delivered to the prostate as the planning target volume [15].

Michelle Stasia *et al.* in 2006 assessed the rectum emptying on dose delivery during three-dimensional conformational radiotherapy for prostate cancer treatment. They showed that the dose delivery variations will reduce if patients vacant their rectums [16].

In 2005, Andre Hille *et al.* examined the effect of variable volumes of rectal balloons on the dose received by the rectum and prostate during conformal radiation therapy for prostate cancer. Their results showed that the use of rectal balloons with volumes of up to 40 ml of air did not lead to a significant advantage in sparing the dose to the rectal wall. However, implementing a rectal balloon filled with 60 ml of air resulted in a significant reduction in the dose delivered to the rectal wall taking into account all clinical target volumes [17].

In 2016, Zhi Chen *et al.* performed a dosimetric study on the different bladder and rectum volumes during prostate cancer radiotherapy. They showed that a 10% increment in bladder volume will cause a 5.6 % reduction in the prescribed mean dose, received by a tumor. Moreover, the changes in the bladder's volume are more effective in comparison with rectum changes during prostate cancer dose delivery. The variations in rectum volume are not significant except for air bubbles, which change the shape of the rectum. Furthermore, they realized that the bladder's volume monitoring will be a crucial issue that should be considered for accurate dose delivery before each irradiation fraction during treatment [18].

In 2020, Om Prakash Gurjar *et al.* accomplished a study on prostate movement due to bladder and rectum changes during image-guided radiotherapy of prostate cancer. They investigated the dosimetric impact of this motion effect on the prescribed dose distributed onto planning target volume and surrounding organs. They showed that the changes in the volume of the bladder and rectum make a significant shift in prostate coordination. They concluded that a proper and strict framework for patients with the empty rectums (and free of air bubbles) and with full bladder should be followed, and daily cone beam computed tomography for positional verification and positioning (before treatment delivery) will be a good standard protocol for accurate dose radiotherapy [19].

At proton therapy of prostate cancer target localization, dose conformity on tumor volume and normal tissue sparing are drastically intensive and significant. Due to these, each possible inter-fractional error caused by bladder volume and rectum filling/emptying in between the courses of treatment may yield serious side effects [20].

Our study aims to quantify the effect of bladder volume changes and also rectum filling/emptying on the dose received by nearby normal tissues surrounding the prostate tumor defined as Planning Target Volume (PTV) in proton radiotherapy, while few studies have been done taking into account protons irradiation as the therapeutic beam. It should be noted that in this work it's assumed that the prostate receives the prescribed dose uniformly without any over- and under-dosage at each volumetric change of bladder and rectum status at treatment fractions.

Our proposed strategy for characterizing and quantifying inter-fractional anatomical changes in the bladder-rectum is assumed to be performed using a typical anthropomorphic phantom. In this way, a variety range of bladder volumes can be finely in access without any concern about additional imaging dose (according to the ALARA principle [21]) that must be received by real patients for detecting each desired bladder volume change.

Furthermore, by implementing our proposed strategy using anthropomorphic phantom, investigation of the effect of bladder and rectum is precisely controllable, since other parameters are constant and independent of current common errors in former literature as: 1) patient-specific motion errors and 2) case-based anatomical variations.

Final results show that a full bladder will cause a dose reduction on normal surrounding tissues such as skin, bladder wall, rectum, and anal canal. But, this reduction is not remarkable if the prostate receives the high prescribed dose with no over- and under-dose. Furthermore, the amount of dose received by the rectum as an organ at risk is not significant while the rectum is full and empty at proton therapy of prostate cancer even by implementing air- or water-filled balloon.

2. Materials and Methods

This analytical study illustrates the effect of volumetric changes in the bladder, rectum, and implemented balloons of doses received by prostate tumor and normal nearby tissues at prostate proton therapy.

2.1. Characterization of Prostate Tumor and Surrounding Tissues at Anthropomorphic Phantom

The current investigation is based on the simulation of our developed anthropomorphic phantom dedicated to the lower part of the thorax region of the patient body. This phantom consists of the prostate tumor, rectum canal, anal canal, and all surrounding normal organs to mimic the real condition. It should be noted that various volumes of the bladder, prostate coordinate, and the status of the rectum and anal canal can be defined at the developed phantom during the simulation process before execution of the code. One of our most challenging issues in this work is to realize precise information for tumor and organ geometries and also materials assignment. This information can be accessible in published literature or performed contributions [22-30]. Furthermore, in this work Ultrasound based images and Computed Tomography (CT) data of real patients with prostate cancers were utilized to remove any possible ambiguity concerning geometrical dimensions and corresponding simulation parameters. This database includes bladder volumes, rectum shape and size, prostate dimension and location, distance from skin to prostate, and also distances between other organs. It should be noted that the Ultrasound system database of four real patients was considered for better assessment with less uncertainty error associated with patient-specific anatomical variations. Moreover, the effect of bladder volume changes on its wall thickness and possible displacement of the prostate tumor was taken into account during the simulation process.

2.2. Characterization of the Proton Beam and Spread Out Bragg Peak (SOBP) Generation

Among different therapeutic beams at radiotherapy, proton therapy technology has been selected for irradiating prostate target volume as PTV, due to its significant treatment efficacy regarding to other common conventional beams. Protons reach to desired kinetic energy by means of accelerating machines such as cyclotrons or synchrotrons. Protons penetrate inside the patient body and deposit their energies inside the patient body according to the Bragg peak concept. For better treatment, required devices are located in front of the beam to modulate the beam, laterally and longitudinally in beam propagation direction to cover tumor volume uniformly in three dimensions (Figure 1). The longitudinal flattening is known as the Spread out Bragg peak [31]. In this way, most of the intensive ionization and hence maximum damage will happen to tumor volume uniformly while other normal nearby tissues will be saved against a high prescribed dose, at the same time [32].

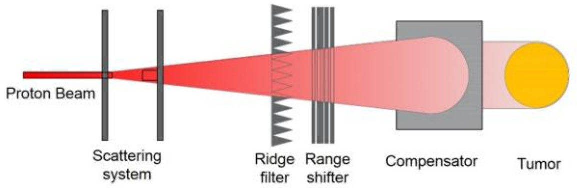

Figure 1. A schematic layout of the proton beam with required modulation devices

In this work, SOBP was generated using modulation of the proton beam energy. In this way, various energies of protons with specific weighting factors have been taken into account and the summation of all produced Bragg curves will result in SOBP with desired flatness as the longitudinal treatment region. To do this, a specific subroutine dealing with source parameters definition was developed at FLUKA code.

Figure 2 shows the Bragg peak curve of protons with 100 MeV as typical energy representing their depth dose distribution inside the soft tissue equivalent phantom.

In order to produce SOBP with a 5 cm flat region, 51 energy modulation was done with equal energy interval (Figure 3).

It should be noted that the flat region shown in Figure 3 will cover prostate tumor volume as PTV that must receive a high prescribed dose during beam irradiation. The defined prostate is a sphere with a 5 cm diameter. From the beam trajectory point of view, the distal and proximal parts of this spherical tumor are at 4 cm and 9 cm depth of patient skin, respectively.

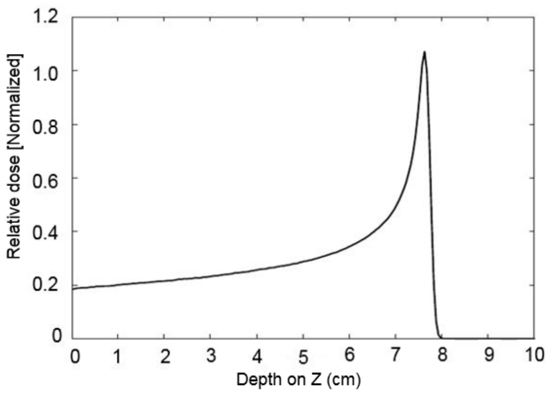

Figure 2. Bragg Peak curve for 100 MeV protons at soft tissue equivalent phantom

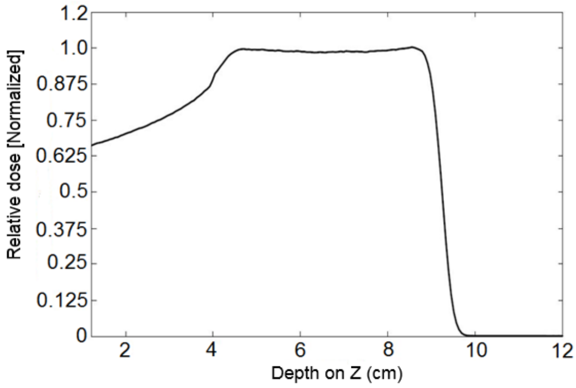

Figure 3. SOPB curve with a 5 cm flat region for covering our proposed prostate target

Figure 4 shows protons dose distribution, two-Dimensionally (2D) along with the Z and X axes. As seen, the treatment region has been depicted as a red square with a 5×5 cm^2 area. The PTV is assumed to be located in this area.

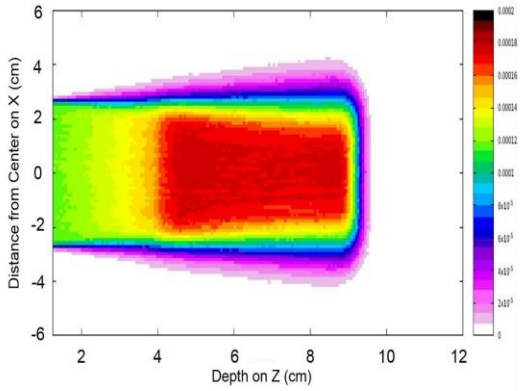

Figure 4. 2D dose distribution of protons on Z and X axes representing red area as treatment region

Figure 5 shows transversal dose profiles in X and Y directions, perpendicular to the beam propagation direction. As seen in this figure, the lateral flat regions are 5 cm (from -2.5 to 2.5 cm) that cover PTV, as well. It should be noted that the penumbra regions of lateral dose profiles will be removed using collimator systems. The latter device, will stop protons at peripheral penumbras and shape the beam transversely, according to the tumor shape, laterally.

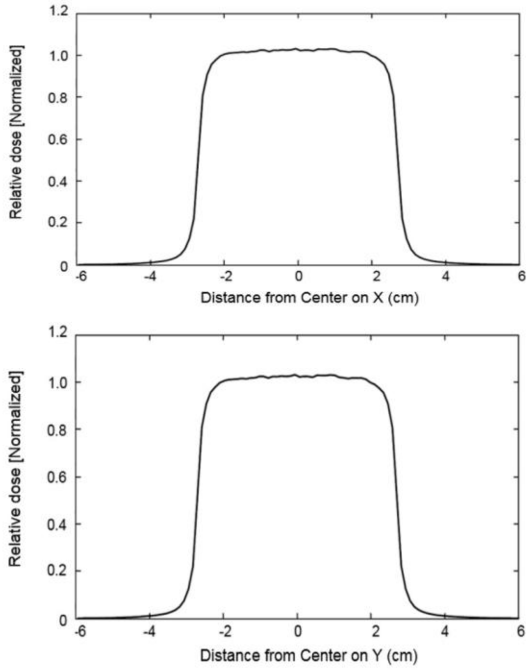

Figure 5. Transversal (lateral) dose profiles with 5 cm treatment flat regions on X (upper) and Y (lower) axes

2.3. FLUKA Code and Simulation Setup

In this study, the Monte Carlo FLUKA code has been used for simulating prostate cancer, skin, bladder, rectum, and other nearby normal tissues by considering all parameters ranging from geometry to material definitions to mimic the real conditions. The required parameters for geometry constructions were checked by Ultrasound based data taken from real patients. It should be mentioned that the FLUKA code is a multipurpose and well-known verified code developed by INFN (in Italy) and CERN (in Switzerland) research centers with various uses in different fields such as particle physics, cosmic ray physics, dosimetry, radiation protection, hadron therapy, space radiation, and accelerator design [22-30].

In our simulation, the material properties (including effective atomic numbers, compound elements, and density) of skin, prostate, bladder, and rectum and other tissues have been defined according to ICRP Report No. 74.

In proton therapy, the main characteristics of a proton beam are its energy and shape. The latter parameter represents the 3D spatial distribution of proton particles that follows from a Gaussian curve with pre-defined FWHM (Full Width at Half Maximum), practically. In another word, in actual conditions, the high energy proton particles exiting from the accelerator are spread as spatial Gaussian distribution function which means protons concentration around the beam central axis is maximum. The divergence degree of the proton beam is assumed to be zero since it is negligible. The distance between the proton beam and the anthropomorphic phantom is 100 cm in air. Since the prostate tumor is assumed to a sphere with a 5 cm diameter located from 4 cm to 9 cm depth from the skin, SOBP with a 5 cm flat region is implemented for prostate bombarding.

Moreover, all displacement and/or deformation of organs or tissues due to volumetric changes of bladder and rectum filling/emptying have been considered based on information extracted from 1) Ultrasound based data, 2) Computed Tomography (CT) data of real patients, and 3) the most important literature performed on prostate motion due to bladder and rectum. For example, bladder wall thickness variations are from 5 to 3 mm while bladder volume ranges from 200 to 600 cc. Table 1 shows a variety of prostate motion studies published formerly in journals with high scientific impacts from 1991 to 2019. It should be noted that in this work the motion and displacement information of the prostate and normal nearby tissues shown in Table 1 has been used while defining geometrical parameters definition during the simulation process.

3. Results

In this work, it’s assumed that prostate tumor as PTV receives prescribed dose uniformly at each volumetric change of bladder ranging from 200 to 600 cc and also rectum status. In other words, patient setup is assumed to be performed correctly to avoid over-under dosage of tumor volume. Taking into account this point, we calculate the dose received by each normal nearby organ during the proton therapy treatment strategy. In this way, a quantitative comparison can be done between the doses delivered to each organ or tissue. It should be noted that the simulation parameters are the same while running at each bladder volume to obtain a reasonable

Table 1. Former literature performed on prostate motion and displacements due to bladder and rectum status (AP: Anterior-Posterior, LR: Left-Right SI: Superior-Inferior)

Number	Author name	Number of patients	Rectum	Bladder	Prostate motion		
					AP (mm)	SI (mm)	LR (mm)
1	Van Herk *et al.*[33]	11	Free state	Full	1SD:2.7	1SD:1.7	1SD:0.9
2	Roeske *et al.* [34]	10	Free state	Full	-0.4±3.9	-0.2±3.2	-0.6±0.7
3	Stroom *et al.* [35]	16	No report	No report	1.7	1.5	0.5
4	Zelefsky *et al.* [12]	50	Free state	Empty	-1.2±2.9	-0.5±3.3	-0.6±0.8
5	Kron [36]	184	No report	No report	1.6	1.5	1.1
6	Zellars *et al.* [13]	24	No report	Full	8	15	0.07
7	Skaresgard *et al.* [37]	46	Full	Empty	2.1	1.9	2.0
8	Leatourneau *et al.* [38]	8	No report	No report	0.9	0.9	No report
9	Cheung *et al.* [39]	33	Empty	Empty	1.8	1.2	0.9
10	Nedereein *et al.* [40]	10	No report	Empty	0.8	1.2	0.2
11	Huang *et al.* [41]	20	No report	No report	1.3	1.0	0.4
12	Britton *et al.* [42]	8	Empty	Full	1.7	1.38	0.7
13	Shimizu *et al.* [43]	10	No report	No report	0.7	0.85	0.6
14	Ten Heken *et al.* [44]	6	Empty	Empty	0.9±2.11	-0.04±0.7	No report
15	Aubry *et al.* [45]	18	Empty	Full	1.4	1.0	0.8
16	Ingrosso *et al.* [46]	10	Empty	Full	0.0±2.07	-0.8±1.28	0.9±0.8

comparison. Our calculations represent the total dose consisting of the therapeutic primary beam and also secondaries (e.g. neutrons) produced due to the inelastic interaction of protons with nuclei of the atoms of 1) the patient body and also 2) modulation devices located in front of the beam [47].

Figure 6 shows the dose received by normal nearby organs while irradiating prostate tumors. These organs are as skin, bladder wall, rectum, and anal canal and their dose can be investigated comparatively, assuming rectum is empty.

It should be noted that the amount of prescribed high dose delivered to prostate tumor is 0.02 GeV/gr per primary particle (with the same weight) at all volumetric changes of bladder ranging from 200 to 600cc. This is due to our assumption taken prior that the target localization has been done without any error during patient setup to avoid under and over dosage of tumor volume. As seen in this Figure, it resulted that the dose received by each surrounding organ is remarkably less than the prescribed high dose (0.02 GeV/gr per primary particle), which proves the robustness of proton therapy technology as a radiotherapy treatment modality.

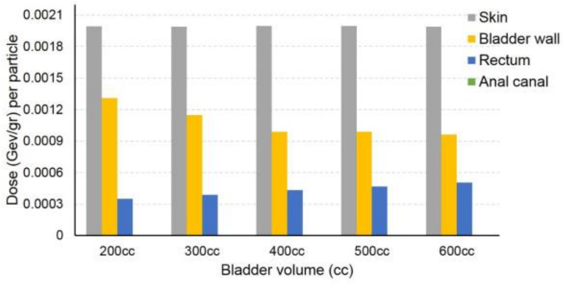

Figure 6. The dose received surrounding organs (bladder wall, skin, rectum, and anal canal) at proton therapy of prostate tumor

Apart from bladder effects, rectum filling/emptying may cause variations in the delivered dose to the normal organs, accordingly.

In order to assess this challenging effect, the amount of dose received by the rectum is calculated assuming it's empty and then full (by soft matter) at two 200 and 600 cc as minimum and maximum volumes of the bladder, respectively (Table 2). As seen in this table, the dose delivered to the full rectum is almost similar to the same calculation while the rectum is empty. It should be noted that the rectum diameter is constant at this comparative assessment and the prescribed high dose is received by prostate volume uniformly.

Table 2. The dose received by the rectum organ at two filling and emptying states of the rectum

Organ	Dose (GeV/gr) per particle (Full rectum)		Dose (GeV/gr) per particle (Empty rectum)	
	Bladder vol. 200 cc	Bladder vol. 600 cc	Bladder vol. 200 cc	Bladder vol. 600 cc
Rectum	3.39E-04	4.93E-04	3.50E-04	5.06E-04

As a final step, the effect of balloon as prostate immobilizer or fixation tool was investigated on dose distribution, numerically. The balloon is first conducted inside the rectum organ from the anal canal to reach the prostate location and then filled with air (pressurized fashion) to push the prostate and make it as a static target while the proton beam irradiates. In this work, the balloon has been simulated at FLUKA code taking into account its actual geometry and material properties to mimic a real condition. Then, the dose received by the rectum is calculated with and without implementing a balloon. It should be noted that the dosimetry impact of balloons on other organs is almost negligible and only the rectum is assumed to be partially influenced.

Table 3 shows the dose received by the rectum (at 600 cc of bladder volume), without and with using a balloon filled with air and water equivalent matter.

With a comparison of the dose received by the rectum with and without the presence of the balloon, it results that balloon influence on dose value is almost negligible.

Table 3. Dose received by the rectum with and without using a rectal balloon

Organ	Dose (GeV/gr) per particle		
	Without balloon	With balloon (air)	With balloon(water)
Rectum	5.06E-04	5.04E-04	4.94E-04

4. Discussion

In proton therapy, a successful treatment significantly depends on filling the gap between prescribed dose distribution and actual dose delivery, while minimizing the dose received by normal surrounding tissues. For this aim, proper target localization and then PTV bombarding can remarkably save healthy organs, mainly for proton therapy of the prostate as a non-rigid dynamic tumor that moves because of bladder and rectum anatomical changes known as inter-fractional motion errors happened in between the treatment sessions. There are many studies focused on measuring prostate displacements originating from bladder volumetric changes and also rectum states (Table 1).

In this work, we investigated the influence of bladder volumetric changes and also rectum filling and/or emptying on the dose delivered to the prostate as PTV and nearby normal tissues in the proton therapy treatment modality. Several studies have been performed on this topic by implementing photon as a therapeutic beam, but there are rare literature dedicated to proton therapy for prostate cancer.

Moreover, it should be noted that in this work we are not looking for under and over dosage of prostate (as PTV) that come from inaccurate target localization and dose conformation. We assumed these two latter issues have already been done with zero error, while the volume of bladder and rectum status is variable at each treatment fraction. Taking this assumption into account, a scientific investigation was done on the amount of dose delivered at each normal surrounding organ around PTV while other performed studies almost include case-based anatomical changes and intra-fractional motion errors, at the same time. Therefore, the obtained results can define an overall framework to quantitatively show the dosimetry impact of each bladder volume and rectum conditions at proton therapy of prostate cancer taking into account that the target localization error is negligible.

Figure 6 shows the dose received by normal nearby organs as a function of bladder volume changes from 200 to 600cc, while irradiating PTV uniformly. These organs are the skin, bladder wall, rectum, and anal canal and their doses can be investigated comparatively, assuming the rectum is empty.

As shown in this figure, the dose received by each surrounding organ (mainly located at the distal part of PTV) is remarkably few in proton therapy in comparison with conventional radiotherapy.

As seen, the dose received by the skin is highest among different organs and the amount of this dose is almost the same at all variations of bladder volumes, which shows that skin dose is independent of bladder and rectum variations and incidence of skin area is equal to two-dimensional beam transversal area at all anatomical variations.

After skin, the bladder wall has received a higher dose and the maximum and minimum dose will reach the wall bladder while the bladder is almost empty (at 200cc) and full, respectively. Because, at a lesser volume of the bladder, the share of bladder wall as incidence organ in front of the incident beam will be increased and vice versa.

As shown in Figure 6, it seems that the rectum and anal canal doses are almost negligible and independent of the bladder volume, regarding skin and bladder wall. This is due to the coordinates of the rectum and anal canal located at a down-stream part of the PTV with specific distances. This causes the rectum and anal canal sparring during proton beam therapy due to the Bragg peak concept. Since the rectum is a critical organ at risk, it can be saved against additional doses, if no over- and under-dosage happened to the prostate target volume.

In this work, we comprehensively considered the rectum a known organ at risk while prostate radiation treatment. Table 2 shows the dose relieved by the rectum under two conditions while the rectum is full and empty at two 200 and 600cc of bladder volume. The main concern was about the secondaries due to the protons' interaction with feces matters inside the rectum. As a result, the amount of this dose is not remarkable at prostate proton therapy in both conditions, while this concern may rise in various treatment modalities using other therapeutic beams. Therefore, there is no concern if patients defecate (rectum emptying) before starting therapeutic irradiation using a proton beam. The same results have been obtained while implementing the balloon inside the rectum although the balloon is used as an immobilized tool to avoid any possible prostate motion or deformation (Table 3). It should be noted that the balloon used clinically are full of no-pressurized air. In this work, a water-filled balloon was simulated as a new proposed strategy to assess the effect of matters inside the balloon. As seen in Table 3, the dose received by the rectum at 3 conditions is the same and non-significant, numerically.

5. Conclusion

Prostate cancer is the second leading cause of cancer death among men in many countries. Depending on the stage of prostate cancer, radiotherapy plays an important role as a treatment modality. Prostate tumor is known as dynamic tumors that move mainly due to inter- and intra-fractional motions that make it problematic during radiotherapy. In this work, a simulation study was done on the effect of bladder volumetric changes and rectum filling/emptying on the amount of dose received by normal nearby organs during radiotherapy with a proton beam utilizing 3 categories of motion database obtained from real patients, to mimic actual condition and reduce numerical uncertainties error during simulations. The simulation environment enables us to precisely investigate the effects of various desired volumes of the bladder on dose distribution while this assessment is almost impossible experimentally on real patients. Final analyzed results showed that the overall dose received by normal nearby organs will be decreased at proton therapy of prostate cancer if the bladder is full. Moreover, rectum filling/emptying and also implementing balloons with different matters have no significant effect on the amount of dose received by this organ. The same strategies can be done using other therapeutic beams in comparative studies. Moreover, the effect of inter and intra-fraction motion errors can be investigated on over and under-dose received by prostate as PTV at hadron therapy, separately.

References

1- Stephanie E Bonn *et al.*, "Physical activity and survival among men diagnosed with prostate cancer." *Cancer Epidemiology and Prevention Biomarkers,* Vol. 24 (No. 1), pp. 57-64, (2015).

2- Jaques Ferlay *et al.*, "Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012." *European journal of cancer,* Vol. 49 (No. 6), pp. 1374-403, (2013).

3- Jacques Ferlay *et al.*, "Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012." *International journal of cancer,* Vol. 136 (No. 5), pp. E359-E86, (2015).

4- Osama Mohamad *et al.*, "Risk of subsequent primary cancers after carbon ion radiotherapy, photon radiotherapy, or surgery for localised prostate cancer: a propensity score-weighted, retrospective, cohort study." *The lancet oncology,* Vol. 20 (No. 5), pp. 674-85, (2019).

5- Michael S Hofman *et al.*, "Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study." *The Lancet,* Vol. 395 (No. 10231), pp. 1208-16, (2020).

6- AJ Hayden, C Catton, and T Pickles, "Radiation therapy in prostate cancer: a risk-adapted strategy." *Current oncology,* Vol. 17 (No. Suppl 2), p. S18, (2010).

7- Felix Böckelmann, Florian Putz, Karoline Kallis, Sebastian Lettmaier, Rainer Fietkau, and Christoph Bert, "Adaptive radiotherapy and the dosimetric impact of inter-and intrafractional motion on the planning target volume for prostate cancer patients." *Strahlentherapie und Onkologie,* pp. 1-10, (2020).

8- Hamid Sarmadi, Rafael Muñoz-Salinas, M Álvaro Berbís, Antonio Luna, and Rafael Medina-Carnicer, "3D Reconstruction and alignment by consumer RGB-D sensors and fiducial planar markers for patient positioning in radiation therapy." *Computer methods and programs in biomedicine,* Vol. 180p. 105004, (2019).

9- Shawn Malone, Juanita M Crook, and Wayne S Kendal, "Respiratory-induced prostate motion: quantification and characterization." *International Journal of Radiation Oncology* Biology* Physics,* Vol. 48 (No. 1), pp. 105-09, (2000).

10- Raymond Miralbell *et al.*, "Dosimetric implications of changes in patient repositioning and organ motion in conformal radiotherapy for prostate cancer." *Radiotherapy and oncology,* Vol. 66 (No. 2), pp. 197-202, (2003).

11- Stefan Wachter *et al.*, "The influence of a rectal balloon tube as internal immobilization device on variations of volumes and dose-volume histograms during treatment course of conformal radiotherapy for prostate cancer." *International Journal of Radiation Oncology* Biology* Physics,* Vol. 52 (No. 1), pp. 91-100, (2002).

12- Michael J Zelefsky *et al.*, "Quantification and predictors of prostate position variability in 50 patients evaluated with multiple CT scans during conformal radiotherapy." *Radiotherapy and oncology,* Vol. 50 (No. 2), pp. 225-34, (1999).

13- Richard C Zellars *et al.*, "Prostate position late in the course of external beam therapy: patterns and predictors." *International Journal of Radiation Oncology* Biology* Physics,* Vol. 47 (No. 3), pp. 655-60, (2000).

14- Paul MA van Haaren, Arjan Bel, Pieter Hofman, Marco van Vulpen, Alexis NTJ Kotte, and Uulke A van der Heide, "Influence of daily setup measurements and corrections on the estimated delivered dose during IMRT treatment of prostate cancer patients." *Radiotherapy and oncology,* Vol. 90 (No. 3), pp. 291-98, (2009).

15- Vitali Moiseenko, Mitchell Liu, Sarah Kristensen, Gerald Gelowitz, and Eric Berthelet, "Effect of bladder filling on doses to prostate and organs at risk: a treatment planning study." *Journal of applied clinical medical physics,* Vol. 8 (No. 1), pp. 55-68, (2007).

16- Michele Stasi *et al.*, "Emptying the rectum before treatment delivery limits the variations of rectal dose–volume parameters during 3DCRT of prostate cancer." *Radiotherapy and oncology,* Vol. 80 (No. 3), pp. 363-70, (2006).

17- Andrea Hille, Heinz Schmidberger, Nadja Töws, Elisabeth Weiss, Hilke Vorwerk, and Clemens F Hess, "The impact of varying volumes in rectal balloons on rectal dose sparing in conformal radiation therapy of prostate cancer." *Strahlentherapie und Onkologie,* Vol. 181 (No. 11), pp. 709-16, (2005).

18- Zhi Chen, Zhaozhi Yang, Jiazhou Wang, and Weigang Hu, "Dosimetric impact of different bladder and rectum filling during prostate cancer radiotherapy." *Radiation Oncology,* Vol. 11 (No. 1), p. 103, (2016).

19- Om Prakash Gurjar, Ramesh Arya, and Harsh Goyal, "A study on prostate movement and dosimetric variation because of bladder and rectum volumes changes during the course of image guided radiotherapy in prostate cancer." *Prostate International*, (2020).

20- Martin Jermann, "Particle therapy statistics in 2014." *International Journal of Particle Therapy*, Vol. 2 (No. 1), pp. 50-54, (2015).

21- Joseph John Bevelacqua, "Practical and effective ALARA." *Health physics*, Vol. 98 (No. 2), pp. S39-S47, (2010).

22- Alfredo Ferrari, Paola R Sala, Alberto Fasso, and Johannes Ranft, "Fluka." *CERN-library in: http://fluka. web. cern. ch/fluka*, Vol. 55 (No. 99), p. 100, (2005).

23- Alfredo Ferrari, Paola R Sala, Alberto Fasso, Johannes Ranft, and U Siegen, "FLUKA: a multi-particle transport code." *Stanford Linear Accelerator Center (SLAC)*, (2005).

24- Giuseppe Battistoni *et al.*, "Applications of FLUKA Monte Carlo code for nuclear and accelerator physics." *Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms*, Vol. 269 (No. 24), pp. 2850-56, (2011).

25- TT Böhlen *et al.*, "The FLUKA code: developments and challenges for high energy and medical applications." *Nuclear data sheets*, Vol. 120pp. 211-14, (2014).

26- Giuseppe Battistoni *et al.*, "The FLUKA code: an accurate simulation tool for particle therapy." *Frontiers in oncology*, Vol. 6p. 116, (2016).

27- Moritz Guthoff, Wim de Boer, and Steffen Müller, "Simulation of beam induced lattice defects of diamond detectors using FLUKA." *Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, Vol. 735pp. 223-28, (2014).

28- S Yalcin, ORHAN Gurler, G Kaynak, and O Gundogdu, "Calculation of total counting efficiency of a NaI (Tl) detector by hybrid Monte-Carlo method for point and disk sources." *Applied Radiation and Isotopes*, Vol. 65 (No. 10), pp. 1179-86, (2007).

29- V Andersen *et al.*, "The FLUKA code for space applications: recent developments." *Advances in Space Research*, Vol. 34 (No. 6), pp. 1302-10, (2004).

30- A Mairani *et al.*, "The FLUKA Monte Carlo code coupled with the local effect model for biological calculations in carbon ion therapy." *Physics in Medicine & Biology*, Vol. 55 (No. 15), p. 4273, (2010).

31- Kine Johnsen, "Simulations of a Therapeutic Proton Beam with FLUKA Monte Carlo Code and Varian Eclipse Proton Planning Software." *The University of Bergen*, (2013).

32- Harald Paganetti, Proton therapy physics. *CRC press*, (2018).

33- Marcel van Herk, Allison Bruce, AP Guus Kroes, Tarek Shouman, Adriaan Touw, and Joos V Lebesque, "Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration." *International Journal of Radiation Oncology• Biology• Physics*, Vol. 33 (No. 5), pp. 1311-20, (1995).

34- John C Roeske *et al.*, "Evaluation of changes in the size and location of the prostate, seminal vesicles, bladder, and rectum during a course of external beam radiation therapy." *International Journal of Radiation Oncology• Biology• Physics*, Vol. 33 (No. 5), pp. 1321-29, (1995).

35- Joep C Stroom *et al.*, "Internal organ motion in prostate cancer patients treated in prone and supine treatment position." *Radiotherapy and oncology*, Vol. 51 (No. 3), pp. 237-48, (1999).

36- Tomas Kron *et al.*, "Intra-fraction prostate displacement in radiotherapy estimated from pre-and post-treatment imaging of patients with implanted fiducial markers." *Radiotherapy and oncology*, Vol. 95 (No. 2), pp. 191-97, (2010).

37- David Skarsgard *et al.*, "Planning target volume margins for prostate radiotherapy using daily electronic portal imaging and implanted fiducial markers." *Radiation Oncology*, Vol. 5 (No. 1), p. 52, (2010).

38- Daniel Létourneau *et al.*, "Assessment of residual error for online cone-beam CT-guided treatment of prostate cancer patients." *International Journal of Radiation Oncology* Biology* Physics*, Vol. 62 (No. 4), pp. 1239-46, (2005).

39- Patrick Cheung *et al.*, "Individualized planning target volumes for intrafraction motion during hypofractionated intensity-modulated radiotherapy boost for prostate cancer." *International Journal of Radiation Oncology* Biology* Physics*, Vol. 62 (No. 2), pp. 418-25, (2005).

40- Aart J Nederveen, Uulke A van der Heide, Homan Dehnad, R Jeroen A van Moorselaar, Pieter Hofman, and Jan JW Lagendijk, "Measurements and clinical consequences of prostate motion during a radiotherapy fraction." *International Journal of Radiation Oncology* Biology* Physics*, Vol. 53 (No. 1), pp. 206-14, (2002).

41- Eugene Huang *et al.*, "Intrafraction prostate motion during IMRT for prostate cancer." *International Journal of Radiation Oncology* Biology* Physics*, Vol. 53 (No. 2), pp. 261-68, (2002).

42- Keith R Britton, Yoshihiro Takai, Masatoshi Mitsuya, Kenji Nemoto, Yoshihiro Ogawa, and Shogo Yamada, "Evaluation of inter-and intrafraction organ motion during intensity modulated radiation therapy (IMRT) for localized prostate cancer measured by a newly developed on-board image-guided system." *Radiation medicine*, Vol. 23 (No. 1), pp. 14-24, (2005).

43- Shinichi Shimizu *et al.*, "Use of an implanted marker and real-time tracking of the marker for the positioning of prostate and bladder cancers." *International Journal of Radiation Oncology* Biology* Physics*, Vol. 48 (No. 5), pp. 1591-97, (2000).

44- RK Ten Haken *et al.*, "Treatment planning issues related to prostate movement in response to differential filling of the rectum and bladder." *International Journal of Radiation*

Oncology• Biology• Physics, Vol. 20 (No. 6), pp. 1317-24, (1991).

45- Jean-Francois Aubry *et al.*, "Measurements of intrafraction motion and interfraction and intrafraction rotation of prostate by three-dimensional analysis of daily portal imaging with radiopaque markers." *International Journal of Radiation Oncology* Biology* Physics*, Vol. 60 (No. 1), pp. 30-39, (2004).

46- Gianluca Ingrosso *et al.*, "Interfraction prostate displacement during image-guided radiotherapy using intraprostatic fiducial markers and a cone-beam computed tomography system: a volumetric off-line analysis in relation to the variations of rectal and bladder volumes." *Journal of cancer research and therapeutics*, Vol. 15 (No. 8), p. 69, (2019).

47- Brenner DJ. Hall EJ. "Secondary neutrons in clinical proton radiotherapy: A charged issue". *Radiotherapy and Oncology*,86: pp. 165-170, (2008).