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Assessing PTV margins in prostate cancer tomotherapy; a comprehensive analysis of interfractional motion and factors affecting prostate and OAR displacement type of study

Vahid Shabaninejad[1], **Ahmad Shanei**[1*], **Mahnaz Roayaei**[2], **Ali Akhavan**[2], **Mohsen Saeb**[2]

[1]Department of Medical Physics, School of Medical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Radiotherapy and Oncology, School of Medical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

***Correspondence to**
Ahmad Shanei, Email: shanei@med.mui.ac.ir

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Abstract

Introduction: Patient adherence to preparation protocols in tomotherapy for prostate cancer is crucial for treatment accuracy.
Objectives: This study aimed to analyze factors affecting prostate displacement, evaluate the required clinical target volume (CTV) to planning target volume (PTV) margins, and assess the impact of patient adherence on treatment precision.
Materials and Methods: This cross-sectional analytical study included 20 prostate cancer patients who underwent tomotherapy from February 2021 to July 2023. Prostate-specific antigen (PSA) levels were measured before treatment, and prostate volume was determined via ultrasound (US). Bladder volume and intestinal cross-sectional area were calculated from megavoltage computed tomography (MVCT) images and compared with CT simulation images. PTV displacement in the anterior-posterior direction was measured, and safety margins were calculated using the formula 2SD ± m. Statistical analyses, including the independent T-test and linear regression were conducted to examine correlations between prostate displacement and changes in rectal and bladder volumes.
Results: A heterogeneous safety margin was determined for three PTVs in the posterior-anterior direction. Bladder and rectal volume changes were significantly associated with prostate displacement. Patient adherence to preparation instructions declined during the second 5-day treatment period, affecting treatment accuracy.
Conclusion: Volumetric changes in the bladder and rectum influence prostate displacement, necessitating the application of heterogeneous safety margins. Ensuring consistent patient adherence, especially in later treatment stages, is essential for maintaining treatment precision. Continuous education and reinforcement of preparation protocols can help mitigate setup uncertainties and improve treatment outcomes.

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Introduction

Prostate cancer (PC) ranks as the second most prevalent malignancy and the third most frequent cause of male mortality globally (1). Helical tomotherapy (HT) represents a highly advanced external beam radiotherapy modality, employing 6-megavolt X-rays for integrated imaging and treatment delivery. Functioning as an intensity-modulated radiotherapy technique, HT utilizes a multi-leaf collimator to modulate the X-ray beams via a sophisticated algorithm (2). This technique facilitates the delivery of a uniform, prescribed dose to the target tissue while minimizing collateral damage to surrounding healthy and sensitive structures (2,3). Dose distribution in the planning target volume (PTV) is obtained by dynamically changing the position of the collimator leaves in a highly complex pattern. According to the definitions of the International Commission on Radiation Units and Measurements (ICRU) in reports 50 and 62, the tumor structure consists of the gross tumor volume (GTV), the clinical target volume (CTV), and the PTV. In radiotherapy treatment planning, the GTV is the visible part of the tumor on CT images, and the CTV includes a margin around the GTV that embraces parts not visible in CT images. The PTV is obtained by increasing the margin to the CTV to encompass tumor movements during treatment, between treatment sessions, as well as random and systematic uncertainties (4,5).

Owing to its anatomical and physiological nature, the prostate gland is prone to movement and displacement during radiotherapy. Multiple factors, including

Key point

Megavoltage computed tomography (MVCT) imaging identifies critical prostate motion patterns for margin customization. Bladder and rectal volume changes significantly influence prostate displacement. Continuous patient education enhances preparation protocol adherence and treatment accuracy.

the patient's position on the treatment table, prolonged treatment, changes in the patient's size and weight, and bladder and rectal fullness or emptiness, can significantly influence the level and direction of prostate displacement. These displacements not only lead to uncertainty in determining the exact position of the tumor but can also introduce systematic and random errors into the treatment process, ultimately affecting the accuracy and effectiveness of radiotherapy (6). It is critical to understand these uncertainties to determine the appropriate margin for PTV to ensure that the target volume receives 95% of the prescribed dose (7).

To minimize uncertainties and reduce side effects, accurate PTV determination is of paramount importance in PC radiotherapy. Modern imaging systems play a pivotal role as powerful tools in augmenting the accuracy of target volume determination. In this regard, four imaging technologies based on megavoltage computed tomography (MVCT), cone-beam computed tomography (CBCT), electronic portal imaging device, and ultrasound (US) have been developed commercially and are used in planning and executing radiotherapy treatment (8).

Objectives

The novelty of this study is to investigate patients' behavior in adhering to pre-radiotherapy preparations throughout the entire treatment period, to evaluate the effect of various factors on prostate displacement, and to determine the optimal PTV margin in helical tomotherapy for PC patients.

Materials and Methods

Patients' data

This descriptive-analytical study enrolled 20 PC patients undergoing tomotherapy at Seyed-al-Shohada hospital in Isfahan between July 2021 and March 2022. To ensure a representative sample, patients with varying clinical characteristics, including age (range: 54–78 years, mean; 67 years), weight, disease stage, Gleason score (9), and prostate-specific antigen (PSA) levels, were included. None of the participants had a history of radical prostatectomy. The Gleason grading system for PC was developed in the late 1960s by Donald Gleason and refined over the next decade. His observations showed that the architectural pattern of the glands in the cancerous tissue was directly related to the prognosis of the disease, and this became the basis for the development of the Gleason grading system (9). By the late 1980s, this system had become the standard pathological grading system for PC (9).

Computed tomography simulator

Before the computed tomography (CT) simulation, patients were provided with a brochure containing preparation instructions and were asked to read it thoroughly and follow its instructions before the CT simulator. According to the standard pelvic scanning protocol, patients were positioned supine on the CT table, with their bladders almost full and their rectums empty. To stabilize the patient during the scan, fixation devices were used between the knees. All patients underwent CT simulation using a SIEMENS Healthineers syngo CT VB20 CT scanner with a 5 mm slice thickness. After the scan completion, permanent tattoos were applied to the patient's skin to be used as a reference for precise patient positioning during subsequent treatment sessions. The obtained CT images were transferred to the treatment planning software to implement target volume contouring for the patients.

Contouring and treatment planning

Precise contouring of anatomical structures, including the prostate, seminal vesicles, rectum, bladder, femoral head, and other organs at risk (OARs), was performed based on CT simulation (CTsim) images according to the RTOG P-0126 treatment protocol. This process was executed by an experienced oncologist using Accuracy Precision treatment planning software version 2.0.1.1. The dose distribution and contouring accuracy were then reviewed and approved by a physicist to ensure the treatment plan quality.

The CTV was determined according to the treatment protocol, and then margins of 4 mm (posteriorly) and 6 mm (anteriorly) were added to it to determine the PTV (10). In the treatment plan design, it was tried to ensure a uniform dose distribution according to the recommendations of the ICRU (11).

Radiotherapy

Patients were advised to adhere to and strictly implement the items in the pretreatment preparation brochure before the radiotherapy session. These instructions included consuming 500 mL of water one hour before treatment, complete bowel evacuation, and partial bladder fullness. They were also recommended to avoid eating flatulent foods to reduce intestinal gas. Patients were positioned supine on the Radiaxact ×9 accuracy tomotherapy bed (12), and their exact position was determined using the apparatus' internal laser system. In addition to initial adjustments based on body tattoos and reference images (offline adjustments), an MVCT image was acquired from the patient at the beginning of each session to perform final adjustments based on the patient's bony anatomy (online adjustments). All adjustments were performed by a radiotherapy technician, and the prescribed dose was delivered to the patient after final confirmation. The total prescribed dose ranged from 50 to 75 Gy and was

delivered to the patients in 25-44 fractions, depending on the disease stage and other clinical factors (10).

Analysis of images and recording of data

In total, 20 CT simulators and 497 MVCTs were analyzed after treatment delivery. In this study, IBM SPSS version 27 software was used for statistical analysis and linear regression. Since prostate displacement tends to be greater in the anterior and posterior directions, prostate motion was examined in the anterior-posterior direction in this study (12). After each treatment session, the information and images of the tomotherapy system were extracted from the system using the MIM image registration and pretreatment evaluation software (MIM Software version 6.8.8) and fused with CT simulator images. To accurately examine the target volume displacement, three specific and similar axial slices were selected in the reference images and MVCT images. In new method, we determined the components of PTV as follows: the first slice included the seminal vesicle (PTVsv, *sv = seminal vesicle*), the second slice was the prostate center (PTVpc, *pc = prostate center*), and the third slice comprised the prostate apex (PTVpa, *pa = prostate apex*). In the extracted images, the MVCT and CTsim images were first examined in three specific and similar slices in terms of bloating or stool and bladder volume. In the case of patient flatulence, the approximate cross-sectional area of the bowel containing flatulence or stool was calculated using the following formula:

$$A = 1/4\pi dAP \times dLR$$

where dAP and dLR are the anterior-posterior and left-to-right diameters, respectively (13). The volume of the cross-sectional area of the bowel containing rectal gas or stool was obtained by multiplying the cross-sectional area of these three slices by the CT thickness (5 mm slice thickness). Next, the bladder volume was obtained using the following formula in CTsim and MVCT images (12);

$$Vol_{bladder} = 1/6\ \pi\ dAP\ (dSI)^2$$

where dAP and dSI are the bladder diameters in the anterior-posterior and superior-inferior (SI) directions, respectively (14). The bladder volume in the CTsim images was subtracted from the MVCT. If the bladder volume in the MVCT images was greater than the reference images, it indicated an increase in the bladder volume on the treatment day compared to the day of the CT simulator (14). Thus, the obtained value is shown with a positive sign and vice versa (Figure 1).

To determine the PTV displacement relative to the bony anatomy, the PTV position was compared in CTsim and MVCT images. Anterior and posterior displacements were recorded with positive and negative signs, respectively. To evaluate patient compliance with the preparation instructions, all treatment sessions for each patient were divided into five equal parts. Then, the standard deviation and the mean value of prostate displacement in each section were calculated and compared with each other (14).

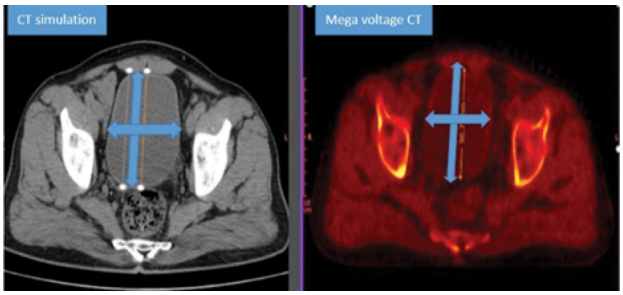

Figure 1. Bladder diameter measurement in two similar slices in CTsim (left) and MVCT (right) images for volume measurement.

Statistical analysis

Statistical analysis was conducted using IBM SPSS version 27. Descriptive statistics (mean ± standard deviation) summarized continuous variables. Given the greater prostate displacement in the anterior-posterior (AP) direction, our primary focus was on AP motion analysis. The independent T-test compared prostate displacement between different adherence groups, while linear regression assessed ($P<0.05$) correlations between prostate displacement and changes in bladder/rectal volumes.

Results

Patients' information

The demographic characteristics of the 20 patients participating in the study are illustrated in Table 1, which includes information about the age, prostate volume, weight, disease stage, Gleason score, and PSA levels of the patients.

Table 2 presents the results of the analysis of 497 MVCT images regarding prostate displacement, examining the mean displacement, standard deviation, and the prostate displacement range in the AP direction. The mean prostate displacement in the AP direction was measured at three different PTV levels. These values are 3.57, 2.58, and 1.20 mm for PTVsv, PTVpc, and PTVpa, respectively. The standard deviations of the displacement at the three PTV levels are 5.25, 4.42, and 2.35 mm, respectively (Table 2).

Periodic evaluation of prostate displacement

The results of the periodic evaluation of the average target volume displacement in all treatment sessions by dividing the entire treatment period into five parts are shown in Figure 2.

Linear regression

The correlation and relationship of prostate displacement with rectal and bladder volumes are shown in Table 3. Since, a $P<0.05$ was considered significant, a significant relationship was observed between the bladder volume

Table 1. The characteristics of the 20 patients that included in the study

No.	Age (year)	Volume of prostate (cc)	Weight (kg)	Stage	Gleason score	PSA (ng/ml)
1	69	53	74	T4	4+4	28
2	54	41	82	N0T4	3+4	52
3	71	51	86	T3a N0	4+5	16
4	61	39	86	T4	3+4	31
5	67	69	72	T3B N0	3+4	34
6	64	58	78	T3a	3+3	25
7	62	58	82	T7	4+4	>100
8	64	38	87	T4	3+4	46
9	71	98	97	T2C N0	3+3	>100
10	68	41	72	T3a N0	5+5	47
11	66	43	72	T4	3+3	12
12	68	41	70	T3aN0b	5+5	47.5
13	71	39	80	T3a N0	3+3	22.8
14	59	97	83	T3aN0b	4+4	20.5
15	71	56	78	T4	5+5	51
16	65	37	80	T3a N0	3+4	>100
17	78	56	75	T3a	5+5	39
18	65	37	80	T3a	4+3	53
19	75	42	102	T2 N0	5+4	7
20	76	39	65	T2C N0	3+4	>100

PSA: Prostate-specific antigen.

and seminal vesicle mean shift, prostate center mean shift, and the apex of prostate mean shift (*P* values: 0.002, <0.001, and 0.003, respectively). Moreover, a significant correlation was found between the rectal volume and seminal vesicle mean shift, prostate center mean shift, and the apex of prostate mean shift (*P* values: 0.009, 0.03, and 0.01, respectively). However, no significant correlations were observed between the prostate volume and prostate displacement in different directions (*P* values: 0.496, 0.576, and 0.643, respectively) (Table 3).

Margin calculation

In Table 4, the margin calculated for the 95% coverage of the prescribed dose is presented based on the formula; M = 2SD ± m.

Discussion

Accurate PTV delineation is crucial in radiotherapy, as any uncertainty at this stage directly affects treatment quality. Overly generous safety margins elevate the risk of acute and late complications in surrounding healthy tissues, whereas insufficient margins increase the likelihood of tumor recurrence. Consequently, precise PTV margin determination is paramount, and systematic errors in this process can significantly compromise treatment outcomes. As expected, a comprehensive assessment of organ motion during radiotherapy extends beyond the PTV (10).

In fact, the planned risk volume (PRV) should also be regarded as an important parameter in the comprehensive evaluation of organ displacements (10). In our previous study (15), we calculated the PTV margin using the van Herk formula. The margin calculated in this paper is larger compared to the margin calculated using the van Herk formula (15). One of our goals was to investigate the dose

Table 2. Statistical results from the analysis of 497 MVCT images

Direction of displacement measurement	Mean shift and direction (mm) ± SD
PTV_{sv} AP	3.57 ± 5.25 anterior
PTV_{pc} AP	2.58 ± 4.42 anterior
PTV_{pa} AP	1.20 ± 2.35 anterior

PTV: Planning target volume; AP: Anterior-posterior.

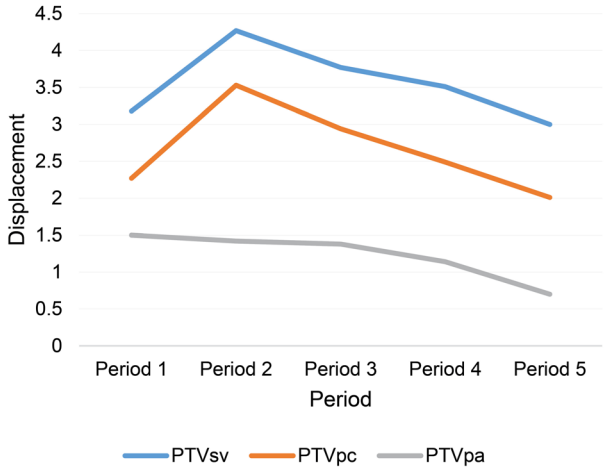

Figure 2. The average displacement of the target volume across five periods of all treatment fractions.

Table 3. Correlation between Prostate Displacement and prostate, bladder and rectal volume (*P* value)

	Seminal vesicle mean shift (*P* value)	Prostate center mean shift (*P* value)	Apex of prostate mean shift (*P* value)
Prostate volume	0.496	0.576	0.643
Bladder volume	0.002+	<0.001+	0.003+
Rectal volume	0.009+	0.03+	0.01+

Note: + indicates a significant relationship between parameters.

Table 4. PTV margin required to cover the prostate displacement with the M=2SD±m formula

Direction of displacement	2SD (mm)	Mean shift date (mm)	PTV margin required to contain 95% of our study sample (mm)
PTV_{sv} anterior	10.50	3.57(anterior)	14.07
PTV_{sv} posterior			6.93
PTV_{pc} anterior	8.84	2.58(anterior)	11.42
PTV_{pc} posterior			6.26
PTV_{pa} anterior	4.70	1.2(anterior)	5.90
PTV_{pa} posterior			3.50

PTV: planning target volume.

index and dose distribution to select the best method for determining the margin. Of course, both formulas used in these two papers are empirical (15). In a previous study, Zhao et al (1) investigated and calculated the PRV margins for the bladder and rectum in the AP and left-right (LR) directions. Their results show that assessing displacements of OARs is essential for the accurate determination of PRV margins at any radiotherapy center (1). In a study by Groher et al (6), around 28 PC patients underwent image-guided radiotherapy (IGRT). In their study, gold core implantation and tattooing were used to ensure accurate patient positioning during treatment. Their results showed that using this method, the required safety margins were determined at 10, 10, and 5.4 mm in the AP, SI, and LR directions, respectively (6). The use of implanted gold cores as visible markers in the PTV considerably increases the accuracy of patient positioning during treatment, which allows for reducing safety margin and, consequently, lowering side effects for the patient (6).

Moreover, Rasch et al (7), presented evidence that the largest uncertainties in the PTV margin resulted from the CTV determination by a radiotherapist, particularly in the AP direction. As reported in the literature, the highest interobserver variability in contouring is in the regions close to the seminal vesicle and the prostate gland. As shown in Table 4, the greatest PTV displacement was observed in the seminal vesicle region because this area is closest to the bladder with the greatest effect from changes in the bladder volume and rectal gas. The appropriate heterogeneous margin for the complete coverage (95%) of the delivered dose was calculated using the formula 2SD ± m (Table 4).

In another study by Oehler et al (16), the PTV margin definition in hypo-fractionated IGRT of localized PC using CBCT for the prostate gland was 7.2 mm, 5.5 mm, 7.1 mm, and 5.5 mm in the anterior, posterior, longitudinal, and lateral directions, respectively (16). In this study, the PTV margins calculated in the anterior and posterior directions were larger than those in the Oehler study because the effect of two important factors, the bladder volume and rectal gas, on prostate displacement was investigated in our study.

Similarly, in the study conducted by Poli et al (8), the PTV margins required to cover prostate displacements in 95% of the positions were 7.7 mm on the right, 6.7 mm on the left, 2.7 mm on the anterior, 14.9 mm on the posterior, 11.1 mm on the superior, and 6.9 mm on the inferior. The margins calculated by their study (8) in the posterior and anterior directions are completely different from this study; since Poli et al (8) studied prostate positioning and adjustments using US, and the influence of the US probe on prostate motion was greater in the posterior direction. Thus, the calculated margin value is greater in the posterior direction, and the obtained results are fully different from this study.

The findings of this study emphasize the critical factors affecting PTV displacement in PC treatment, particularly the roles of bladder and rectal fullness or emptiness. These results are in line with previous studies showing that changes in these anatomical structures can significantly affect prostate position during radiotherapy sessions. Additionally, Maruoka et al (13) examined the correlation between age, weight, bladder volume, prostate volume, rectal volume, prostate displacement, and the margin required to achieve 90% dose coverage during IGRT. In their study, 586 MV-CBCT scans were analyzed, and the

mean calculated margin was 4.6 mm anteriorly, with a range of 1.4–17 mm, and 3.1 mm posteriorly, with a range of 0.8–6.9 mm. The study also showed a positive correlation between rectal volume and the required posterior margin (13). The recent study by Arumugam et al (17) indicated that smaller treatment margins (≤ 3 mm) could effectively reduce genitourinary and gastrointestinal toxicities, thus endorsing the need for accurate margin determination based on the real-time monitoring of organ positions. The recommendation to define PTV margins heterogeneously, specifically, 6.93-14.07 mm for the seminal vesicle, 6.26-14.07 mm for the prostate center, and 3.5-5.9 mm for the prostate apex, represents a proper approach that pays attention to individual patient anatomy and treatment dynamics (17). These findings correspond to those of Winter et al (18) who reported that using modern imaging techniques, such as cone beam CT, could reduce PTV margins compared to traditional methods based solely on bony anatomy.

The statistical results of this study indicate that only 14% of treatment sessions were performed according to the planned protocol, signifying a considerable incidence of non-compliance (18). This evidence agrees with the findings of Fleshner et al (19), who emphasized that patient non-adherence to preparation protocols can result in substantial deviations in treatment outcomes. The need for ongoing patient education and re-education to ensure adherence throughout the treatment process was emphasized in their review.

The observation that approximately 82% of displacements occurred in the anterior direction further highlights the need for patient positioning strategies (19). The magnitude of the largest displacement related to the seminal vesicle suggests that this region is more sensitive to changes in bladder and rectal volumes, which was also examined in studies by Yartsev et al (20). These findings emphasize the need for continued adjustments in treatment planning based on real-time data to increase the accuracy of dose delivery. Furthermore, our results imply that patient education on dietary management and adherence to preparation instructions is essential to reduce displacements and optimize treatment outcomes. This is in line with a previous study by Er et al (21), who accentuated the importance of adherence strategies in improving treatment effectiveness in patients with advanced PC.

According to the measurements in Figure 1, the highest prostate displacement was observed in the second treatment period, followed by a decrease in the prostate displacement. In this regard, the lowest prostate displacement occurred in the fifth treatment period. Our results indicated that physicians and medical staff should provide re-education to patients on strict adherence to instructions after the end of the first five treatment days to avoid the occurrence of undesirable displacements.

Baker and Behrens (22) reported that interpersonal movement could significantly affect treatment outcomes. They emphasized the need for careful monitoring and necessary adjustments during treatment and concluded finally that intrapersonal movement tends to increase over time, indicating that longer treatment duration can exacerbate displacement problems. This finding corresponds to our results, where the highest displacement occurred in the second treatment period, probably resulting from factors such as patient positioning and physiological changes (22).

The observed reduction in prostate displacement over successive treatment fractions may be attributed to improved patient adherence to preparation protocols or to physician adjustments based on accumulated treatment data. This hypothesis is corroborated by studies highlighting the importance of continuous patient education regarding bladder and rectal filling protocols, which are crucial for minimizing prostate motion (23,24).

In this study, the limitations of measuring prostate displacement are clearly evident in the lateral and SI directions, as this study did not use fiducial markers on the prostate, and adjustments were performed based on tattoos and bony anatomy. Therefore, it was not possible to measure displacements in the lateral and SI directions.

Conclusion

Precise determination of the PTV and appropriate safety margins is crucial in radiotherapy planning, directly impacting treatment quality and patient outcomes. This study's findings highlight the need for careful and continuous monitoring of organ motion, particularly in sensitive regions such as the seminal vesicles and prostate, to minimize both tumor recurrence and treatment-related toxicities. Advanced imaging modalities and patient education regarding dietary management can further enhance treatment accuracy and mitigate complications. Moreover, reinforcing adherence to treatment protocols and providing re-education after the initial treatment phase are essential for minimizing organ displacements and optimizing treatment outcomes.

Limitations of the study

This study was limited by its small sample size and single-center design, which may affect generalizability. Additionally, reliance on MVCT for displacement measurements and variability in patient adherence to preparation protocols could influence margin accuracy.

Authors' contribution

Conceptualization: Vahid Shabaninejad, Ahmad Shanei.
Data curation: Vahid Shabaninejad, Mahnaz Roayaei, Ali Akhavan.
Formal analysis: Vahid Shabaninejad, Mohsen Saeb.
Funding acquisition: Ahmad Shanei.
Investigation: Vahid Shabaninejad, Mahnaz Roayaei, Ali Akhavan, Mohsen Saeb.
Methodology: Vahid Shabaninejad, Ahmad Shanei.
Project administration: Ahmad Shanei.
Resources: Mahnaz Roayaei, Ali Akhavan.
Software: Vahid Shabaninejad.

Supervision: Ahmad Shanei.
Validation: Ahmad Shanei.
Visualization: Mahnaz Roayaei.
Writing–original draft: Vahid Shabaninejad.
Writing–review & editing: Ahmad Shanei, Mohsen Saeb.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Isfahan University of Medical Sciences (Ethical code #IR.MUI.MED.REC.1401.003). Prior to any intervention, all participants provided written informed consent. The study was extracted from PhD thesis of Vahid Shabaninejad in the department of Medical Physics at this university. The authors have fully adhered to ethical issues, such as plagiarism, data fabrication, and double publication.

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