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BIOPHYSICS AND MEDICAL PHYSICS

Robustness of Radiotherapy Plans to Geometric Uncertainties in Irradiating Patients with High-Density Prostheses

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Abstract—The concept of introducing additional target margins has proven effective in photon radiotherapy and, therefore, is a widely accepted method for ensuring the required dose distribution during planning. However, due to the specific interactions of photon radiation with matter in cases of significant tissue heterogeneity, radiotherapy planning necessitates assessing the robustness of the plan or developing a plan resilient to existing dose delivery uncertainties. This study tested the robustness of radiotherapy plans to geometric uncertainties using two irradiation technologies: CRT (conformal radiation therapy) and IMRT (intensity-modulated radiation therapy). A total of 15 patient plans with metallic prostheses were analyzed. The patient's position relative to the isocenter of the irradiation beams was geometrically shifted to simulate potential patient setup errors. Data on actual displacements obtained during pretreatment visualization—approximately 25 000 treatment fractions for patients with various tumor localizations—were analyzed. According to the results of the study, the probability of not achieving the required dose distribution for the clinical target volume is no more than 0.04 ± 0.03 % when using the CRT technique and no more than 7 ± 4% when using IMRT. Thus, the CRT plans demonstrated greater robustness with respect to the target compared to IMRT plans. When IMRT techniques are required for treating patients with prostheses, increased attention must be paid to the patient's setup and plan robustness verification.

Keywords: radiation therapy, robustness, patient setup errors, geometric uncertainties, CRT, IMRT, prosthesis

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INTRODUCTION

Errors in planning and conducting external beam radiotherapy can lead to undesirable dose distributions delivered to the patient. Such errors include inaccuracies in imaging data and planning software, limited precision in setting up the accelerator beam, patient setup errors, and anatomical changes. Therefore, treatment planning must be aimed at creating plans that are robust to uncertainties [1]. Currently, the concept of introducing additional margins during target irradiation is widely used in radiotherapy. CTV represents the clinical target volume that accounts for potential microscopic tumor spread and serves as the irradiation target from a clinical perspective. The problem of geometric uncertainties associated with the irradiation setup, patient positioning, and organ motion is traditionally addressed by expanding the irradiation field around the target. This is achieved by adding a margin around the CTV to form the PTV—the planned target volume. A robust plan must satisfy two conditions: first, the CTV must receive the prescribed dose despite possible errors; second, constraints for normal tissues must be met regardless of potential planning or dose delivery errors. Treatment planning is aimed at ensuring that the PTV receives the prescribed dose. It is assumed that as long as the CTV moves only within the PTV, the prescribed dose is delivered to the CTV [2]. The required margin for the CTV is determined by the magnitude of errors, leading to the development of general recommendations for PTV construction [3–5]. Reports 50, 62, and 83 of the International Commission on Radiation Units and Measurements [6–8] also provide guidelines for constructing the CTV and

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PTV. The established concept of additional margins (CTV-PTV margin concept) is based on approximating a statistical dose cloud resulting from the relative insensitivity of megavoltage photon dose distribution to density changes along the beam path. That is, minor changes in patient position or anatomy do not significantly affect dose distribution. With this approximation, the theory consistently yields good results in photon radiotherapy for relatively homogeneous media [9]. Studies [4, 10] have shown that the dosimetric accuracy criterion of ±5 %, recommended by the International Atomic Energy Agency (IAEA) [11], is met for at least 90% of patients. According to the 2020 ESTRO survey, 97% of photon centers in Europe and Central Asia use PTV-based optimization methods [12], which can be attributed to the efficiency of this approach. However, considering the specific interactions of photon radiation with highly heterogeneous tissues, treatment planning within the PTV concept can yield inaccurate results. First, photon passage through matter is characterized by an attenuation coefficient that depends on the properties of the medium and the photon energy [13]. Due to changes in the attenuation coefficient with increasing electron density, the dose begins to drop more rapidly with depth, leading to a dose decrease beyond the region of high electron density heterogeneity. Second, due to differences in material density, stopping power, and multiple scattering of secondary electrons, local dose maxima occur at the transition from less dense to denser media, and minima occur at the transition from denser to less dense media. For photon beams with energies in the 4 to 20 MeV range typically used in radiotherapy, the magnitude of the maximum at the soft tissue interface can reach 30% [14]. These effects, occurring at the boundary of media with different electron densities, can lead to significant dose distribution changes when planning in the presence of geometric shifts of the target relative to the beam. Therefore, due to the specific interactions of photon radiation in highly heterogeneous tissues, it can be assumed that radiotherapy planning in such cases requires special attention, specifically assessing plan robustness or developing a robust plan. Treatment plan robustness can also depend on the irradiation technique. IMRT plans are implemented using photon beam intensity modulation. The dose distribution is strictly geometrically constrained, and the number of photons reaching the patient's body per unit time is modeled based on the target shape, patient position relative to the beam, and tissue density distribution in the irradiated volume [15]. As a result, IMRT plans may exhibit lower robustness to geometric shifts, which can be attributed to the specific features of the technique, although high tissue heterogeneity may also contribute. The dose in IMRT plans is calculated at each point, taking into account the density of tissues, so even a small target shifts relative to the field can result in unplanned absorbed dose distribution in adjacent regions, leading to underdose and overdose zones within the target. For example, when the patient shifts into a region where the prosthesis is supposed to be located according to the plan, soft tissues may occupy that region. This increases the likelihood of overdosing tissues adjacent to the prosthesis. Conversely, the traditional CRT technique may demonstrate greater robustness in the considered clinical scenarios due to the absence of intensity modulation to compensate for tissue heterogeneity [16, 17]. The aim of this study is to investigate the robustness of CRT and IMRT plans to changes in the patient's setup relative to the isocenter of the beams in the presence of a high-density prosthesis in the irradiation area.

1. MATERIALS AND METHODS

Uncertainties in radiotherapy are typically divided into systematic components, arising from errors in pretreatment imaging and thus common to all treatment fractions, and random components for each fraction, arising from daily patient positioning procedures [4, 18]. The primary contributor to variations in photon dose distribution is geometric error, which includes patient setup errors and changes in patient geometry during treatment (e.g., interfractional and intrafractional organ motion) [2, 9]. Therefore, this study considers scenarios of uncertainty modeled by geometric displacements of the target along three axes: x (lateral), y (vertical), and z (longitudinal).

To account for the probability of each scenario, it is necessary to determine the distribution of displacements. Due to computational demands, many studies [1, 2, 9, 19] have used a limited set of discrete errors—random geometric displacements of the target or sampled errors from a normal distribution—to analyze plan robustness or create robust plans.

Since this method of error assessment depends on the sample (in particular, on the irradiation region), this study analyzed a database from the Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, which contains data on patient displacements relative to a reference value obtained directly before treatment. Several main tumor localization areas were considered: head (9.265 values), neck (263 values), head–neck (1.024 values), chest (3.106 values), abdominal cavity (2.133 values), pelvis (1.796 values), and extremities (567 values). The analyzed displacement values were subjected to statistical analysis based on calculating the frequencies of displacements observed in intervals of 0.1 mm within the range of −10 mm

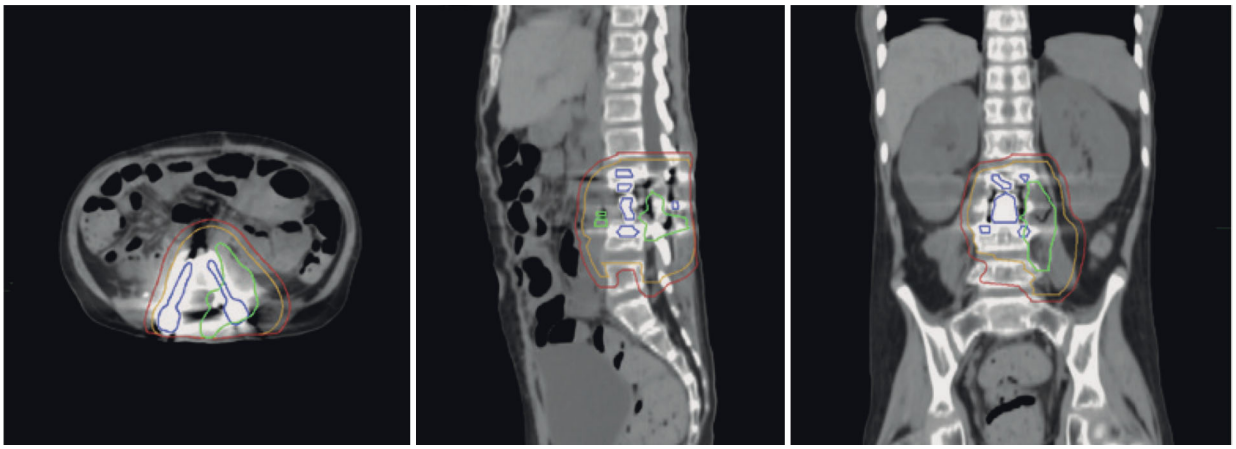

Fig. 1. Example of a CT scan of a patient with a prosthesis: blue contour—prosthesis, green contour—GTV, yellow contour—CTV, red contour—PTV.

to 10 mm. As a result, displacement distributions were constructed for each irradiation region and displacement direction, and the data were approximated using OriginLab Origin 2022. To assess robustness to geometric uncertainties, treatment plans for 15 patients with high-density metallic prostheses were analyzed (an example CT image is shown in Fig. 1). The dose in each plan was calculated using the MIM SureCalc® Monte Carlo method with a specified statistical error of 1% for 18 additional treatment scenarios, generated by shifting the plan's isocenter in three directions (6 shifts along x, 6 ones—along y, and 6 ones—along z). Plans with irradiation energies of 6/10 MeV were used. Prostheses in the selected plans were made of titanium and various metal alloys (stainless steel, chromium alloys, cobalt alloys, etc.). The relative electron density of the materials required for dose calculation was determined in the planning system using an extended curve for converting Hounsfield units (CT numbers) to relative electron density values. Standard margins of 6 mm from the CTV were used for constructing the PTV in the considered irradiation localizations (abdominal cavity, pelvis, and extremities), although this value can vary depending on the clinical situation. The dose-volume histogram (DVH) points $D2$, $D5$, and $D10$, characterizing the behaviour of dose distribution maxima, and $D90$, $D95$, and $D98$, characterizing the behaviour of dose distribution minima, were analyzed, along with the mean dose value D_{mean} for structures such as the CTV and organs at risk. For each parameter considered (DVH points and mean dose D_{mean}), relative dose changes (in %) were calculated for the selected displacements.

Table 1. Standard deviations of displacement distributions for various irradiation localizations

Localization	Displacements, mm		
	lateral	vertical	longitudinal
Head	0.94 ± 0.01	0.95 ± 0.01	1.25 ± 0.01
Neck	1.30 ± 0.09	2.32 ± 0.21	2.10 ± 0.16
Head–Neck	1.09 ± 0.03	0.91 ± 0.21	1.15 ± 0.03
Chest	1.77 ± 0.04	1.63 ± 0.04	2.31 ± 0.05
Abdominal cavity	1.71 ± 0.03	1.34 ± 0.03	2.31 ± 0.06
Pelvis	1.83 ± 0.05	1.91 ± 0.05	2.39 ± 0.07
Extremities	1.69 ± 0.08	1.89 ± 0.08	1.90 ± 0.07

2. RESULTS

Displacement distributions of patient positions were obtained for various tumor localizations (head, neck, head–neck, chest, pelvis, abdominal cavity, and extremities). The determined distributions have an average adjusted determination coefficient (Adj. R-square) of 92% with a Gaussian function (based on approximation in OriginLab Origin 2022). Examples of the obtained displacement distributions with their approximations are shown in Fig. 2. Standard deviations for the displacement distributions of the considered localizations are presented in Table 1.

The obtained data indicate that the largest deviations for most irradiation regions occur along the couch direction (z). For example, the standard deviations for the pelvic region in the right–left and up–down directions are 1.83 ± 0.05 mm and 1.91 ± 0.05 mm, respectively, while in the couch direction, they are 2.39 ± 0.07 mm. The smallest standard deviations are observed for the head region, with values of 0.93 ± 0.01 mm for the right–left direction, 0.94 ± 0.01 mm for the up–down direction, and

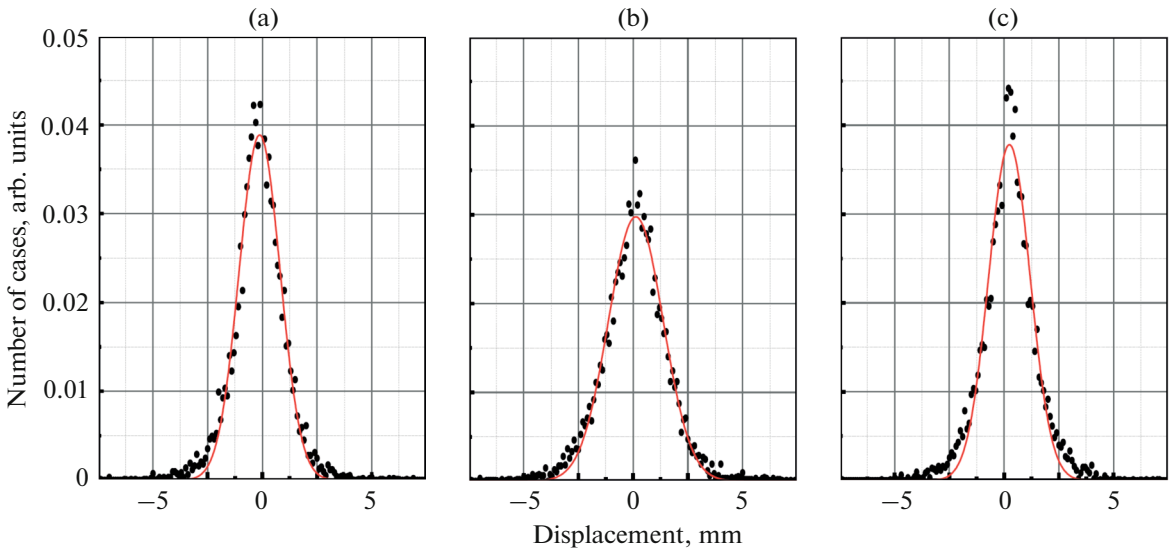

Fig. 2. Examples of patient displacement distributions: head, displacement direction: (a) lateral, (b) longitudinal, (c) vertical (dots—values obtained from analyzing the table with real patient setup data, red line—Gaussian function approximation of the data in OriginLab Origin 2022).

1.25 ± 0.01 mm for the couch direction. This illustrates that rigid fixation of the head using individually shaped thermoplastic masks can achieve high reproducibility in patient setup. To analyze plan robustness to displacements, the dose in each plan was recalculated for displacements of one (σ), two (2σ), and three (3σ) standard deviations in three directions (x, y, z). Displacements by σ (2σ and 3σ) have different absolute values (in mm) for different irradiation regions, but the displacements within the intervals $[-\sigma;\ \sigma]$ (similarly for $[-2\sigma;\ 2\sigma]$ and $[-3\sigma;\ 3\sigma]$) occur with the same probability. Therefore, using displacements in units of σ rather than absolute units allows us to generalize the data across all patients with various tumor localizations and draw overall conclusions about the robustness of plans with prostheses to geometric uncertainties.

Data for 15 patients were divided into two groups: CRT and IMRT (DMLC (dynamic multileaf collimation) + VMAT (volume-modulated arc therapy)) to evaluate the more robust method. For CRT plans, data were averaged across 12 cases, and for IMRT across three cases. For each group, dose dependences (specifically, the dose at the considered DVH points—$D2$, $D5$, $D10$, $D90$, $D95$, $D98$, and the mean dose D_{mean}) normalized to the dose in the nondisplaced position were plotted as a function of displacements in units of σ. An example of such dependences is shown in Fig. 3.

To ensure tumor control, a dose delivery accuracy of 5% to the target volume is required [11]. According to the analysis of CRT plan data, CTV coverage (DVH point $D98$) remains at an acceptable level in all considered uncertainty scenarios, with a reduction of no more than 0.5%. For IMRT plans, displacements of 3σ in all three directions and 2σ in two axes (x and z) fail to provide the required dose distribution for the CTV. Additionally, IMRT plans exhibit greater changes in dose maxima compared to CRT: the dose near the prosthesis may increase by more than 5% for displacements of 3σ (see Table 2 and Figs. 3a–3d). Thus, the analysis of the results showed that IMRT plans are less robust with respect to dose distribution in the target.

The results for displacements of σ, 2σ, and 3σ (Table 2) allow for estimating the probability that the necessary dose distribution will not be achieved in the CTV, based on the properties of the normal distribution and assuming equal probabilities for all displacement directions. This probability is calculated using the formula:

$$P = \sum_{i=1}^{3} p_i \left[\int_{-\infty}^{-7/2\sigma} f(x)\,dx + \sum_{j=-3}^{3} \left(\delta_{ij} \int_{(j-1/2)\sigma}^{(j+1/2)\sigma} f(x)\,dx \right) + \int_{7/2\sigma}^{+\infty} f(x)\,dx \right], \quad (1)$$

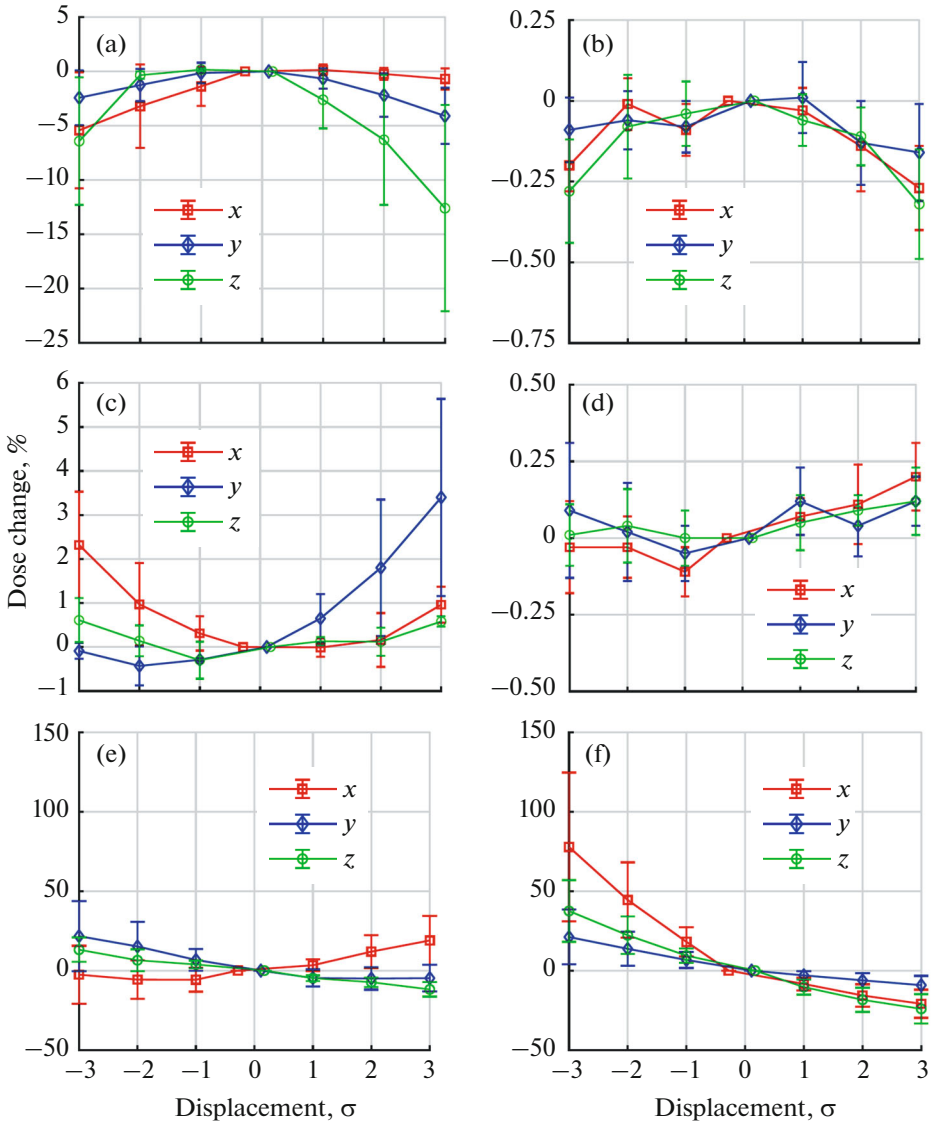

Fig. 3. Dose changes (in %) depending on the magnitude of isocenter displacement (summarized data for 15 patients): (a) DVH point D98 for CTV, IMRT; (b) DVH point D98 for CTV, CRT; (c) DVH point D2 for CTV, IMRT; (d) DVH point D2 for CTV, CRT; (e) DVH point D2 for the organ at risk (bladder), IMRT; (f) DVH point D2 for the organ at risk (bladder), CRT.

where $p_i = 1/3$ represents the probability of a displacement occurring along one of the three axes (assuming equal probabilities for all directions, with p_1, p_2, and p_3 corresponding to displacements along x, y, and z, respectively); $f(x)$ represents the Gaussian function approximation of the displacement distribution; the sum over $j = \overline{-3;3}$ is the result of numerical integration of the Gaussian function at points from -3σ to 3σ, corresponding to the midpoints of segments of length σ within the range $[-7\sigma/2;\ 7\sigma/2]$. The first integral accounts for the probability of displacement in the interval $(-\infty, -7\sigma/2]$, the integrals in the sum over j account for the probability of displacement in discrete sections within $[-7\sigma/2,\ 7\sigma/2]$, and the third integral accounts for the probability of displacement in the interval $(7\sigma/2, +\infty)$; δ_j takes the value 0 if the dose change for displacements at all considered DVH points does not exceed 5% and the value 1 if the dose change for displacements at any of the considered DVH points exceeds 5%. Thus, when calculating the probability that the required dose distribution will not be achieved in the CTV using formula (1), the probabilistic contribution of each considered uncertainty scenario is taken into account based on the magnitude of the patient position displacement.

The study of cases involving a target near the boundary of tissues with different electron densities

Table 2. Maximum dose changes ΔD in displaced CRT and IMRT plans (in %) based on DVH data for CTV (values not meeting the 5% accuracy criterion are highlighted in bold)

Displacement	ΔD in CRT plans, %			ΔD in IMRT plans, %		
	x	y	z	x	y	z
-3σ	-0.2 ± 0.1	0.1 ± 0.2	-0.3 ± 0.2	$\mathbf{-5.0 \pm 5.0}$	-2.4 ± 2.5	$\mathbf{-6.0 \pm 6.0}$
-2σ	-0.1 ± 0.2	0.2 ± 0.3	-0.1 ± 0.2	$\mathbf{-3.0 \pm 4.0}$	-1.6 ± 1.5	2.7 ± 0.3
$-\sigma$	-0.2 ± 0.2	0.2 ± 0.2	-0.1 ± 0.2	1.8 ± 1.4	-0.7 ± 0.6	0.6 ± 0.3
σ	-0.3 ± 0.2	0.1 ± 0.1	0.1 ± 0.2	0.3 ± 0.5	1.6 ± 1.0	-2.6 ± 2.6
2σ	-0.1 ± 0.1	-0.3 ± 0.2	-0.1 ± 0.1	2.2 ± 1.5	$\mathbf{4.0 \pm 2.0}$	$\mathbf{-6.0 \pm 6.0}$
3σ	-0.3 ± 0.1	-0.2 ± 0.2	-0.3 ± 0.2	$\mathbf{4.3 \pm 1.6}$	$\mathbf{7.0 \pm 3.0}$	$\mathbf{-13.0 \pm 10.0}$

showed that the probability of not achieving the required dose distribution in the CTV during CRT is no more than $0.04 \pm 0.03\%$, while for IMRT, it is no more than $7 \pm 4\%$ (probabilities were calculated using formula (1)).

Additionally, analysis of dose distributions revealed that IMRT plans are more robust to displacements concerning organs at risk: dose changes are several times smaller than those in CRT plans. For CRT, the dose in organs at risk, such as the bladder, rectum, kidneys, etc., may increase by more than 80% (see Figs. 3e–3f). However, it is challenging to determine what percentage change in the initial dose is critical, as the dose to the organ at risk in the undisplaced plan can vary significantly between patients. Nonetheless, the high probability of increased dose burden must be considered, as reducing dose exposure to healthy tissues and organs is one of the primary goals of radiotherapy.

CONCLUSIONS

Analyzing treatment plan robustness provides a more comprehensive understanding of the delivered dose in the presence of uncertainties related to patient positioning. This study employed one method for assessing plan robustness to geometric uncertainties, which demonstrated that in treatment plans for patients with prostheses, the target may be irradiated with less accuracy than the recommended 5% threshold set by the IAEA [11]. Therefore, for patients with a prosthesis located near the tumor, the use of CRT plans may be recommended, provided that the planning objectives can be achieved. However, there are cases where the proximity of organs at risk to the target volume, the radioresistance characteristics of specific organs, the overall clinical picture, and challenges in ensuring adequate target coverage may render the use of CRT plans unacceptable. Consequently, if a specific clinical case necessitates the use of an IMRT plan, heightened attention must be paid to patient setup, with corrections to patient positioning performed before each treatment session, and the plan must be prevalidated for robustness to geometric uncertainties.

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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