Scientific Article

Effect of Body Mass Factors on Setup Displacement in Gynecologic Tumors and Subsequent Effect on PTV Margins

Zaheeda Mulla, BTech,[a,][*] **Rania Hashem, MD,**[b] **Abdullah AlMohamad, NDRT,**[a] **Amina Weber, NDRT,**[a] **Hanadi Habibullah, MD,**[a] **Ghassan Abdulmoula, BSc,**[a] **Mohamed G. Mohiuddin, BSc,**[b] **and Reem Ujaimi, MD**[c]

[a]*Department of Oncology, King Faisal Specialist Hospital and Research Center-Jeddah, Jeddah, Saudi Arabia;* [b]*Department of Radiology, King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia; and* [c]*Department of Radiology, Faculty of Medicine, King Abdul-Aziz University, Jeddah, Saudi Arabia*

Abstract

Purpose: This study aimed to analyze the effect of body mass factors (BMFs) on setup errors in gynecologic tumors, and whether the planned tumor volumes (PTVs) are adequate for obese patients.
Methods: This was a retrospective study of 46 consecutive female patients with gynecologic tumors who were treated with volumetric modulated arc therapy. Setup accuracy was verified using daily cone beam computed tomography. Accuracy was determined for each fraction by testing 2 different PTVs (cutoff I = $\leq$0.7 cm; cutoff II = $\leq$1.0 cm). A pooled analysis was conducted to test the association between accuracy levels (within vs beyond PTV) and the mean and variance of body mass index (BMI), umbilical (UC), and hip circumference (HC). A receiver operating characteristics curve analysis was carried out to test the sensitivity of BMI, UC, and HC in predicting inaccurate setup.
Results: A significant association between BMFs and level of accuracy was observed in the lateral and vertical directions, but not in the longitudinal direction. In the lateral direction, inaccurate setups were associated with a greater BMI (mean difference: $\sim$3.50 kg/m^2; P = .001), UC ($\sim$10 cm), and HC ($\sim$8 cm) compared with accurate setups (P < .001). With respect to the vertical direction, inaccurate setups (>0.7 cm margin [cutoff I]) were associated with a greater BMI (mean difference = 7.4 kg/m^2; P = .001), UC (5.3 cm; P < .001), and HC (16.0 cm; P < .001) with reference to accurate setups. The receiver operating characteristics curve analysis showed that a BMI >31.4 kg/m^2 was predictive for inaccurate setup in the vertical direction with 90.0% sensitivity with respect to cutoff I. Furthermore, a BMI >30.3 kg/m^2 was predictive for inaccurate setup in the lateral direction with 92.5% sensitivity with respect to cutoff II.
Conclusions: The accuracy of radiation therapy setups for gynecologic tumors is highly sensitive to patients' BMI, notably in the lateral and vertical directions. We suggest that daily cone beam computed tomography should be applied on patients with a BMI >30.3 kg/m^2, using customized protocols that are lower in dose and comparable in image quality.

Introduction

Gynecologic tumors, including uterine, cervix, and ovarian cancers, are among the 10 most common tumors in Saudi women[1] and the leading causes of lethality

among women globally.[2] The majority of these patients require postoperative radiation therapy (RT), notably for high-grade tumors.[3,4] With advancing RT techniques, such as intensity modulated RT, a more accurate delineation of target volumes is required, emphasizing the need for accurate daily setup and immobilization to reduce setup errors.[5]

Guidelines set by the Radiation Therapy Oncology Group for gynecologic tumors established 2 different clinical tumor volumes (CTVs) depending on the bladder being full or empty. The volume resulting from the combination of the above 2 volumes was defined as the internal target volume.[6] In a study conducted by the authors, 2 different immobilization devices for RT treatment of pelvic cancer were compared, and gynecologic tumors and obesity were determined to be associated with greater setup errors in translational directions.[7] Subsequently, the authors turned their focus on gynecologic tumors to determine the magnitude of setup displacement in relation to body mass factors (BMFs) and its effect on the aforementioned target volumes.

Substantial evidence has shown that obesity represents a challenge in the RT of gynecologic cancers.[8] Obese patients and patients with a large hip circumference (HC) and umbilical anterior−posterior diameter had greater setup displacements,[9-13] because treatment requires daily imaging to ensure reproducibility of setup. Otherwise, expanding the target volumes may be necessary, especially where daily imaging is not practicable, which is the case in settings with reduced resources or high patient flow or particular circumstances, such as the coronavirus disease 2019 pandemic.[14]

This study analyzed the effect of 3 different BMFs, including BMI, HC, and umbilical circumference (UC), on setup errors in gynecologic tumors, attempting to determine the optimum PTV as a function of patient corpulence. The study hypothesis was that setup errors increase with BMFs, notably in the translational shifts; thus, obese women require greater margins for PTV compared with their nonobese counterparts. The following objectives were explored: Analysis of the association between setup errors and all 3 BMFs; determination of BMI, UC, and HC thresholds beyond which the used PTV margins are not compatible, and testing of the sensitivity of these thresholds.

Methods

Design and Setting

A retrospective study was conducted in the Radiation Oncology Unit. The study protocol was reviewed by the institutional review board, which provided ethical approval.

Participants

The study included data from 46 consecutive women with endometrial or cervix cancer treated with curative volumetric modulated arc therapy (VMAT), with or without surgery, between 2020 and 2021. Patients with other pelvic tumors and those treated with palliative RT were not included.

Treatment Planning

Before computed tomography (CT) simulation, all patients were given instructions to empty their bowels, and drink a fixed amount of water after emptying their bladder. Patients were in the supine position, with their head on a pillow, arms on the chest (patients with para-aortic involvement had arms above the head), and legs positioned using a low dual-leg positioner fixed to the treatment couch, with an indexing bar to minimize setup errors. An anterior−posterior tattoo and 2 lateral tattoos were placed at the level of the pubis (most stable point), using setup lasers, to facilitate daily setup reproducibility. For para-aortic involvement, an additional tattoo was placed anteriorly at the level of the inferior umbilicus. A CT scan was performed using 3-mm slice thickness. The CTV was defined per the Radiation Therapy Oncology Group guidelines, with an expansion of 0.7 cm and 1 cm for the PTVs for organ motion and setup errors.

Daily Imaging

All patients underwent a pre-RT assessment of setup accuracy in the supine position (same as in CT simulation), using daily kV cone beam CT imaging (after aligning tattoo marks on patients to lasers, and implementing shifts to isocenter per the plan). The acquired images were registered by a qualified therapist to the planning reference image to determine the corresponding translational and rotational shifts compared with the adjacent bony and soft tissues. Initial alignment was to the bone for nodal involvement, followed by a soft-tissue match for the vaginal cuff. Where the bladder or bowel was noncompliant, the patient was removed from the treatment couch, and asked to drink more water, defecate, or get rid of gas, as required. Patients were setup again afterward.

All shifts were computed by shifting the treatment couch. The shifts defined as setup errors were recorded and analyzed by systematic and random errors as described previously[7] through the 6 directions (lateral, vertical, and longitudinal, and X, Y, and Z rotational axes).

Patients' weight and height were measured to calculate the body mass index (BMI). In addition, BMI, UC, and HC were measured at baseline and the 10th and 20th fractions. Other BMFs, including umbilical anterior−posterior and lateral diameters and hip anterior−posterior and lateral

diameters, were only measured at baseline. Weight was measured to the nearest 0.1 kg using an electronic scale, and the other anthropometric indices were measured on cone beam CT images to the nearest 0.1 cm. BMI was categorized as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥ 30.0 kg/m^2). UC and HC were analyzed as continuous variables.

Statistical Methods

The data were collected, the database was cleaned and coded, and the variables were calculated in Microsoft Excel. Descriptive and analytic statistical analyses were performed with the Statistical Package for Social Sciences, version 21.0, software for Windows (SPSS Inc; Chicago, IL). Categorical variables are presented as frequency and percentage, and continuous variables are presented as mean ± standard deviation (SD).

Average absolute shifts were calculated separately for all fractions in the translational and rotational directions for both systematic and random errors by transforming negative into positive values in the translational directions, and large values into absolute values (360-raw value) in the rotational directions. Additionally, translational and rotational total vector errors (TVEs) were estimated to determine the overall shift in the 3 translational and 3 rotational directions from the simulation isocenter, and were calculated as follows:

Translational TVE

$$= \sqrt{(lateral\,shift^2 + longitudinal\,shift^2 + vertical\,shift^2)}$$

$$Rotational\,TVE = \sqrt{(X^2 + Y^2 + Z^2)}$$

Linear regression was used to analyze the relationship of translational and rotational TVEs with the BMFs. The results are depicted as unstandardized regression coefficient (B) with 95% confidence interval (CI), and the goodness-of-fit measure is expressed by squared Pearson's coefficient (R^2). Accuracy was determined for each fraction by testing 2 different cutoffs in translational shifts, including ≤ 0.7 cm and ≤ 1.0 cm. Accuracy rates were calculated by direction, in systematic and random settings separately, and were computed for each patient as the percentage of fraction shifts within the PTV, defined as +0.7 cm (cutoff I) and +1.0 cm (cutoff II) margins of the CTV for translational shifts and +3 for rotational shifts. The mean ± SD of accuracy rates was calculated, and bivariate intercorrelations were analyzed with respect to each translation cutoff using Pearson's correlation.

In addition to baseline measures, measures of BMI, UC, and HC were repeated at the 10th and 20th fractions for 31 and 29 of 46 patients, respectively. To analyze the correlation of accuracy in translational

directions with 3 BMFs, a pooled database was generated. This pooled database was comprised of shifts of the first 20 fractions, coded as 1 for translational shifts within tye PTV (ie, accurate) and 0 for those beyond the PTV (inaccurate), along with the corresponding BMI, UC, and HC values. For patients with repeated measures, measured values of BMFs at baseline, as well as those at the 10th and 20th fractions, were matched with the corresponding shifts, and intermediate shifts (ie, fractions 2-9 and 11-19) were matched with estimated values of BMI, UC, and HC assuming a linear change between the measured values at baseline and the 10th fraction and between the 10th and 20th fractions, respectively.

For patients without repeated measures of BMFs (previous cone beam CT images not available to extract data), only the 1st fraction's data were matched with baseline measures of BMFs. Thus, the acquired database was comprised of pooled data for 3 BMFs, including BMI (n = 584), UC (n = 615), and HC (n = 615) and 2 accuracy rates with respect to the 2 PTV cutoffs (≤ 0.7 cm and ≤ 1.0cm) for each to the 3 translational directions, including lateral (n = 841), longitudinal (n = 841), and vertical (n = 838). An independent t test was used to compare the means and variations of the BMFs of shifts within versus those beyond the PTV.

Furthermore, a receiver operating characteristics (ROC) curve analysis was performed to analyze the validity of BMI, CU, and HU in predicting inaccurate settings (beyond PTV) in the significant directions. The data are presented as area under the curve (AUC) with standard error and 95% CI. Additionally, the best cutoff was determined by calculation of Youden's index using the ROC curve coordinate points, and the sensitivity and specificity of the determined cutoff was calculated. For all statistical tests, $P < .05$ was considered to reject the null hypothesis.

Results

Baseline Patient Clinical and Anthropometric Characteristics

The mean age of patients was 55.54 years (SD: 14.12 years). The majority of patients had cervix cancer (63.0%) and received a total RT dose of 45 Gy (63.0%). The mean BMI was 31.67 kg/m^2 (SD: 7.71 kg/m^2), with the majority being overweight (26.1%) or obese (56.6%). Other anthropometric measures are depicted in Table 1.

Average Absolute shifts and Total Vector Errors

Translational shifts were larger and with a higher variance in lateral and longitudinal directions (mean: ≥ 0.45;

Table 1 Baseline participant clinical and anthropomorphic characteristics (N = 46)

Parameter		Mean	Standard deviation
Age, y		55.54	14.12
Height, cm		154.51	6.91
Weight, kg		75.86	20.10
Body mass index, kg/m^2		31.67	7.71
Umbilical anterior−posterior diameter, cm		24.41	4.56
Umbilical lateral diameter, cm		35.82	5.45
Hip anterior−posterior diameter, cm		23.68	4.47
Hip lateral diameter, cm		37.93	5.84
Umbilical circumference, cm		102.41	17.43
Hip circumference, cm		108.64	14.17
Parameter	Category	Frequency	Percentage
Body mass index	Underweight (<18.5 kg/m^2)	1	2.2
	Normal (18.5-24.9 kg/m^2)	7	15.2
	Overweight (25.0-29.9 kg/m^2)	12	26.1
	Class I obesity (30.0-34.9 kg/m^2)	12	26.1
	Class II obesity (35.0-39.9 kg/m^2)	9	19.6
	Class III obesity (≥40.0 kg/m^2)	5	10.9
Diagnosis	Cervix	29	63.0
	Endometrium	17	37.0
	Intact	21	45.7
	Postoperative	25	54.3
Total dose, Gy	45	29	63.0
	54	1	2.2
	55	1	2.2
	57	15	32.6
Number of fractions	25	46	100.0
Dose per fraction, Gy	1.80	29	63.0
	2.16	1	2.2
	2.20	1	2.2
	2.30	15	32.6

SD: ≥0.23) compared with the vertical direction (mean: ≤0.29; SD: ≤0.16) when considering both systematic and random settings. The mean TVE was 0.86 (SD: 0.34) and 0.79 (SD: 0.30) in the systematic and random settings, respectively (Table 2).

Correlation of Total Vector Errors with Body Mass Factors

BMI was significantly correlated with random translational TVE in a weakly positive relationship (B = 0.013; 95% CI, 0.002-0.025; and R^2 = 0.119; P = .019). UC was correlated with translational TVE in a weakly positive relationship (B = 0.005; 95% CI, 0.001-0.010; and R^2 = 0.090; P = .042). No other significant relationship of translational or rotational TVEs was observed with any of the BMFs (Table 3).

Accuracy Rates and Intercorrelations

By focusing on translational directions, accuracy rates were lower in the lateral and longitudinal directions with respect to the systematic and random settings using both accuracy cutoffs I (≤0.7 cm) and II (≤1.0 cm) compared

Table 2　Average absolute shifts and total vector errors

Setting/plan	Direction	Mean	Standard deviation
Systematic settings			
Translational	Lateral	0.49	0.28
	Longitudinal	0.46	0.32
	Vertical	0.29	0.16
Rotational	X	1.32	0.85
	Y	0.91	0.47
	Z	0.74	0.39
Random settings			
Translational	Lateral	0.46	0.23
	Longitudinal	0.45	0.23
	Vertical	0.24	0.09
Rotational	X	1.26	0.55
	Y	0.86	0.35
	Z	0.77	0.27
Total vector error			
Translational−systematic	0.86	0.34	
Translational−random	0.79	0.30	
Rotational−systematic	1.97	0.82	
Rotational−random	1.93	0.51	

Values are average absolute shifts in cm for translational shifts and degree in rotational shifts. $P < .05$ is considered a statistically significant difference.

with the vertical direction. Shifts in the lateral and longitudinal directions were positively correlated with one another, with the strongest correlation ($R = 0.574$; $P < .001$) observed in random settings using accuracy cutoff I (Suppl. Material 1).

Association of BMI, UC, and HC With Setup Accuracy in Translational Directions−Pooled Analysis

With respect to the lateral direction, the pooled analysis showed a higher mean BMI in inaccurate setups compared with accurate setups, with a mean difference of approximately 3.50 kg/m^2, and was statistically significant using both cutoffs ($P = .001$). Similarly, measures of UC (mean difference ~10 cm) and HC (~8 cm) were significantly higher in inaccurate setups compared with accurate setups ($P < .001$; Table 4).

With respect to the vertical direction, BMI (mean difference = 7.4 kg/m^2; $P = .001$), UC (5.3 cm; $P < .001$), and HC (16.0 cm; $P < .001$) were higher in inaccurate versus accurate setups, but only using cutoff I. When using cutoff II, only HC showed a statistical significance, with a mean difference of 11.7 cm between inaccurate and accurate setups ($P = .041$; Table 4).

Accuracy of BMI, UC, and HC in Predicting Inaccurate Setup in Lateral and Vertical Plans

The ROC curves are depicted in Figure 1, and the corresponding statistics, as well as the BMI, UC, and HC cutoff calculations with their respective sensitivity and specificity levels, are depicted in Table 5. With respect to cutoff I, BMI was predictive of inaccurate (beyond PTV) setup with an AUC of 0.609 and 0.673 in the lateral and vertical directions, respectively. The corresponding BMI cutoffs were estimated at >30.4 kg/m^2 and >31.4 kg/m^2, predicting an inaccurate setting in the 2 respective directions with 78.1% and 90.0% sensitivity, respectively. With respect to cutoff II, BMI was predictive beyond PTV setup in the lateral direction with an AUC of 0.680, and a BMI >30.3 kg/m^2 was associated with inaccurate settings with 92.5%.

The AUCs and cutoffs calculated on UC and HC showed lower sensitivity in indicating inaccurate setting.

Table 3   Linear correlation of total vector errors with different body mass factors with regard to systematic and random settings

Parameter	Setting	Translational shifts					Rotational shifts				
		B	95% CI		R^2	*P* value	B	95% CI		R^2	-value
Body mass index	Systematic	0.009	−0.005	0.022	0.037	.197	0.008	−0.024	0.040	0.006	0.613
	Random	0.013	0.002	0.025	0.119	.019*	−0.002	−0.022	0.018	0.001	.817
Umbilical circumference	Systematic	0.004	−0.002	0.010	0.043	.167	0.000	−0.014	0.015	0.000	.944
	Random	0.005	0.001	0.010	0.090	.042*	−0.005	−0.014	0.004	0.026	.284
Hip circumference	Systematic	0.006	−0.001	0.013	0.063	.092	0.000	−0.018	0.017	0.000	.969
	Random	0.006	0.000	0.012	0.081	.055	−0.006	−0.017	0.005	0.025	.296
Umbilical anterior−posterior diameter	Systematic	0.013	−0.009	0.036	0.032	.231	−0.003	−0.058	0.051	0.000	.911
	Random	0.011	−0.009	0.031	0.029	.260	−0.022	−0.055	0.012	0.037	.202
Umbilical lateral diameter	Systematic	0.011	−0.008	0.030	0.032	.235	0.010	−0.036	0.055	0.004	.662
	Random	0.011	−0.006	0.027	0.037	.198	−0.020	−0.047	0.008	0.043	.165
Hip anterior−posterior diameter	Systematic	0.019	−0.003	0.041	0.063	.093	−0.002	−0.057	0.054	0.000	.950
	Random	0.012	−0.008	0.032	0.034	.219	−0.006	−0.041	0.029	0.003	.727
Hip lateral diameter	Systematic	0.015	−0.002	0.032	0.070	.075	−0.003	−0.045	0.040	0.000	.899
	Random	0.011	−0.004	0.026	0.047	.148	−0.017	−0.043	0.009	0.038	.197

Abbreviations: CI, confidence interval; B, unstandardized regression coefficient; R^2, Pearson's coefficient; * statistically significant difference (P<.05)

Table 4 Comparison of body mass factors by accuracy level in translational directions (pooled analysis)

Parameter	Setup accuracy	Direction								
		Lateral			Longitudinal			Vertical		
		Mean	SD	*P*-value	Mean	SD	*P*-value	Mean	SD	*P*-value
Cutoff I: ≤0.7 cm										
Body mass index, kg/m^2	Inaccurate	35.01	6.82		32.97	9.06		39.31	9.26	
	Accurate	31.67	8.04	.001*	31.95	7.80	.330	31.91	7.86	.001*
Umbilical circumference, cm	Inaccurate	109.41	14.44		101.22	18.66		116.51	17.34	
	Accurate	100.44	16.02	< .001*	101.61	15.73	.835	101.21	15.89	< .001*
Hip circumference, cm	Inaccurate	116.75	14.01		110.79	16.23		126.26	12.64	
	Accurate	109.73	15.08	< .001*	110.59	14.98	.918	110.23	14.97	< .001*
Cutoff II: ≤1.0 cm										
Body mass index, kg/m^2	Inaccurate	35.53	5.02		31.70	8.59		35.01	5.05	
	Accurate	31.73	8.14	.001*	32.11	7.90	.733	32.06	8.00	.331
Umbilical circumference, cm	Inaccurate	111.18	13.70		99.49	18.86		106.94	13.11	
	Accurate	100.54	16.00	< .001*	101.76	15.79	.336	101.54	16.13	.378
Hip circumference, cm	Inaccurate	118.15	13.05		108.61	15.99		122.24	10.81	
	Accurate	109.81	15.12	< .001*	110.81	15.03	.322	110.50	15.12	.041*

Abbreviations: PTV, planning treatment volume; SD, standard deviation

The analysis concerned the pooled data from the first 20 fractions by considering the respective changes in the 3 body mass factors. Setup accuracy is defined regarding the shift value with respect to the used cutoff for the PTV, as follows: Inaccurate setup = shift beyond PTV; accurate = shift within PTV. Test used: Independent *t* test.

* Statistically significant result (*P* < .05)
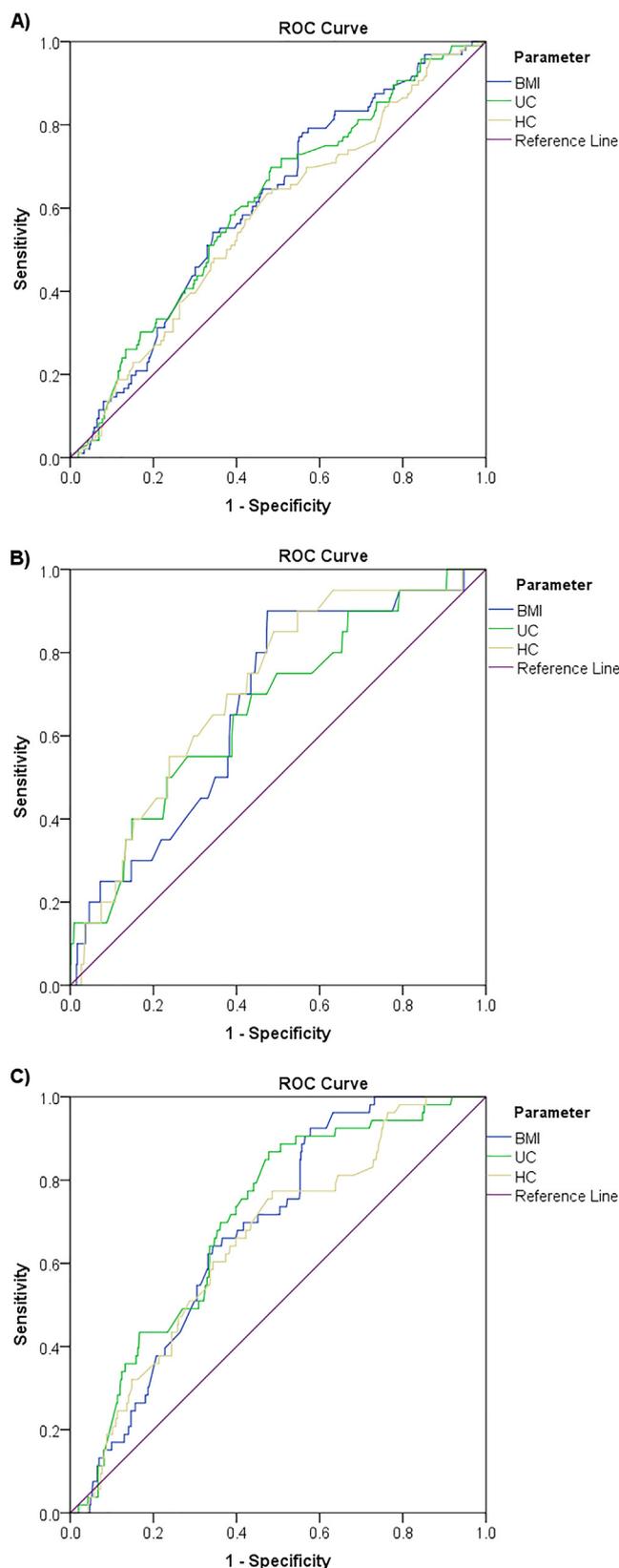
Fig. 1   Receiver operating characteristics curves of inaccurate setup in translational shifts as a function of body mass factors, including body mass index, umbilical circumference, and hip circumference, with respect to a planning target volume of 0.7 mm in the (A) lateral and (B) vertical directions, and a planning target volume of 7 mm in the (C) lateral direction. The analysis used the pooled data from the first 20 fractions, considering the respective changes in the 3 body mass factors.

Table 5 Accuracy of pooled setups regarding planning treatment volume as a function of body mass index, umbilical circumference, and hip circumference (receiver operating characteristics curve analysis, cutoffs, and corresponding sensitivity and specificity)

Direction (setup error cutoff)/predictor	Receiver operating characteristics curve analysis					Best predictor cutoff		Diagnostic value	
	Area under the curve	Standard error	95% confidence interval		P-value	Cutoff	Youden's index	Sensitivity	Specificity
A. Lateral (>0.7 cm)									
BMI, kg/m^2	0.609	0.030	0.551	0.668	.001*	30.4	0.222	78.1	44.1
UC, cm	0.610	0.031	0.550	0.670	.001*	99.5	0.215	69.8	51.7
HC, cm	0.576	0.031	0.515	0.638	.019*	109.9	0.161	47.4	52.6
B. Vertical (>0.7 cm)									
BMI, kg/m^2	0.673	.055	0.565	0.781	.009*	31.4	0.426	90.0	52.6
UC, cm	0.667	.061	0.547	0.786	.011*	108.9	0.268	55.0	71.8
HC, cm	0.710	.053	0.606	0.814	.001*	109.9	0.360	85.0	51.0
C. Lateral (>1.0 cm)									
BMI, kg/m^2	0.680	0.031	0.621	0.740	< .001*	30.3	0.347	92.5	42.3
UC, cm	0.704	0.033	0.639	0.768	< .001*	99.6	0.522	86.8	52.2
HC, cm	0.654	0.036	0.583	0.725	< .001*	109.1	0.288	77.4	51.4

Abbreviations: BMI, body mass index; HC, hip circumference; UC, umbilical circumference

The analysis used the pooled data from the first 20 fractions by considering the respective changes in the 3 body mass factors. Test used: Independent *t* test.

* Statistically significant result ($P < .05$)

For all the above-mentioned estimates, specificity was low (up to 52.6%), except for UC in the vertical direction (71.8% for cutoff >108.9 cm).

Effect of Operative Status on Setup Error

There was no difference between intact and operated pelvises with regard to the mean systematic or random setting or TVE in any of the directions (Suppl. Material 2). However, in the pooled analysis, accuracy rates in the longitudinal direction were lower in intact versus operated patients, using both ≤0.7 cm (79.0% vs 85.3%; $P = .017$) and ≤1.0 cm (89.8% vs 94.9%; $P = .005$) cutoffs, respectively (Suppl. Material 3).

Discussion

Key Observations

The present study tested the effect of 3 BMFs on the magnitude of setup errors in female patients treated with VMAT, with or without surgery, for endometrial or cervix malignancy. The greatest displacements were observed in the lateral and longitudinal directions. Shift magnitudes in the lateral and longitudinal directions were correlated with one another when considering both the systemic and random settings. Although the accuracy rates in the lateral and longitudinal plans were correlated with one another, the association between setup accuracy and BMFs was significant in the lateral, but not the longitudinal, direction. In the vertical direction, although setups were highly accurate (92.8% using cutoff I; 98.6% using cutoff II), the variance in setup error was significantly associated with BMI, UC, and HC with respect to cutoff I, but not cutoff II. BMI was the most accurate indicator for setup inaccuracy.

Radiation Therapy Setup Errors in Gynecologic Tumors

Findings from the present study show that patients treated with VMAT for gynecologic tumors are subject to great setup errors in the translational direction, both in the systematic and random settings. Most remarkably, the shift's magnitude was significant in the lateral and longitudinal directions, showing the lowest accuracy notably using a PTV margin of 0.7 cm (cutoff I ≤ 0.7 cm), where the accuracy rates were 77.6% and 77.5%, respectively. Of note, with automatic couch adjustment after cone beam CT, patients were all treated within the PTV. On the other hand, setup error was remarkably low in the vertical direction.

These setup variations in patients treated for gynecologic tumors are due to the large motion of pelvic organs, both during inter- and intrafraction times.[15] Furthermore, the data demonstrated that the magnitude of the shift depends on the organ, because uterine motion is larger than cervix motion as one would expect conforming to the anatomic features of each organ,[16,17] would have significant effect on the definition of RT target volumes. Comparing setup errors between patients with cervix versus endometrial cancer was beyond the scope of the study.

Several authors were concerned with the frequency and magnitude of setup errors in gynecologic tumors. However, the differential magnitude between the directions varied between the studies. For instance, Haslam et al. observed an average setup error ranging from 0.19 to 0.26 mm in systematic and 0.26 to 0.37 cm in random settings, and the error magnitude was the greatest in the anterior−posterior (vertical) direction.[18] Similarly, Laursen et al. found the greatest setup error (0.36 mm) in the anterior−posterior direction with a CTV-PTV margin as high as 1.16 cm versus 0.82 and 0.96 cm in the superior−inferior and mediolateral direcdtions, respectively.[19]

Santanam et al. found average setup errors ranging from 0.15 to 0.46 mm in systematic settings and from 0.31 to 0.48 in random settings, and the superior-inferior direction entailed the greatest displacement with a CTV-PTV margin as high as 0.94 cm, compared with 0.72 and 0.67 cm in the anterior-posterior and mediolateral, respectively (20). Therefore, determining the treatment margins that encompass these setup errors while sparing normal tissue is critical. However, there is no consensus regarding the margins of the PTV to be used in patients with gynecologic cancers.[19-22] Repeated cone beam CT imaging remains a precious tool to enhance the precision of treatment targeting.[12]

Effect of Body Mass Factors on Translational Shifts

The present study demonstrated the significant contribution of BMFs, including BMI, UC, and HC, in enlarging setup errors in the translational direction among patients treated for cervical and endometrial cancers. Since the authors observed that setup errors were of greater magnitude and variance in the lateral and longitudinal directions and significantly correlated with one another, they hypothesized that such a variance may be explained by the variance in BMI and other BMFs. However, the effect of BMFs was only significant in the lateral direction, but not the longitudinal direction, which indicates that BMI, UC, and HC account for the magnitude and variance of the setup errors in the lateral direction, but they do not affect setup errors in the longitudinal direction. Also, setup errors in the vertical direction were proportional to

BMI, UC, and HC with respect to cutoff I, but not cutoff II, although settings in this direction were highly accurate (92.8% using cutoff I; 98.6% using cutoff II).

The effect of BMI and other BMFs on the magnitude of setup errors was demonstrated in gynecologic tumors, and probably contributes to the unfavorable outcomes in obese patients.[23] In agreement with the study findings, Lin et al. reported a gradual increase in translational setup errors in patients treated for endometrial malignancy as a function of the BMI category. On the other hand, the authors did not observe a significant correlation between BMI category and rotational shifts. By using the median BMI, the authors found that BMI $\geq$30 kg/m^2 increased the percentage of patients who would require a +0.7 cm margin shift from 11% to 28% in the vertical, 5% to 15% in the longitudinal, and 6% to 25% in the lateral direction, with reference to BMI <30kg/m^2.[11]

Similarly, Kim et al. analyzed the effect of BMI on setup errors in the 3 translational directions among 52 women with different gynecologic cancers, including cancer of the endometrium, cervix, and vulva. The results demonstrated that patients with BMI $\geq$30kg/m^2 had a greater CTV-to-PTV margin, notably in the medial−lateral direction (10.3 vs 7.3 mm), compared with those who had a BMI <30 kg/m^2. Furthermore, the authors reported that the proportion of patients with a shift $\geq$0.5 cm was greater in the high-BMI subgroup (62%) compared with the normal-BMI group (48%).[24] Likewise, Bray et al. demonstrated that patients with BMI $\geq$30 kg/m^2 displayed a greater composite shift in the translational direction (8.0 $\pm$ 5.8 mm) compared with those with BMI <30 kg/m^2 (5.5 $\pm$ 3.2 mm), and BMI explained 57% of the variance of the shift in the right−left direction. The authors concluded on the importance of daily image guided RT for obese patients to reduce imprecision in dose and volume delivery.[25]

On the other hand, few studies failed to demonstrate such an effect of BMFs on setup errors. For example, Haslam et al. observed no statistically significant effect of BMI, weight, or height on setup errors in a sample of participants composed of 15 normal-weighted, 12 overweight, and 15 obese patients.[18] The variability of the effect between the studies may be affected by the considered BMF, in addition to several technical and methodological factors, such as the sampling methods, immobilization technique, and/or characteristics of the population, notably the organ and operative status.

Considering Body Mass Factors in Defining Shift Margin

Altogether, these data demonstrate the relevance of considering further adjustment for organ displacement in obese patients, which may have an effect, not only on the efficacy, but also the safety of RT. Amini et al.

demonstrated that a patient with BMI $\geq$30kg/m^2 had a 5-fold risk of having a translational shift $\geq$0.7 cm, showing the necessity of increasing the PTV for such patients beyond the 0.7 cm standard.[9]

Interestingly, Yavas et al. explored the association of BMI with both PTV and organ-at-risk volumes in patients with early stage endometrial cancer who were treated with adjuvant RT subsequent to a total hysterectomy. The analysis focused on comparing field-in-field RT to 3-dimensional conformal RT in terms of precision of treatment delivery. Although the authors reported a positive relationship of BMI with PTV and mean irradiation doses received by the organs at risk, field in field was observed to significantly reduce the organ-at-risk volumes in obese patients, notably for those with bowel, bladder, and bone marrow cancer.[26]

Furthermore, what applied to gynecologic cancers applied also for other pelvic cancers. Wu et al. explored the relationship of different BMFs with setup errors in patients treated for rectum, prostate, and gynecologic cancers. The authors found a positive linear relationship between UC and systematic and random setup errors in the translational direction, which was stronger in the mediolateral direction irrespective of the organ.[13]

Body Mass Index Was the Most Accurate Indicator for Setup Inaccuracy

The particularity of the present study was the determination of BMI, UC, and HC cutoffs based on the ROC curve analysis, but most other studies used an arbitrary cutoff of $\geq$ 30kg/m^2.[11,24,25] Despite using a different method, the study analysis showed a similar cutoff value, because a BMI >30.3 kg/m^2 was predictive for inaccurate setup (shift >1.0 cm) in the lateral direction with 92.5% sensitivity, which corresponds to the obese category defined by the World Health Organization classification.[27] Moreover, a BMI >31.4 kg/m^2 was predictive for an inaccurate setup (shift >0.7 cm) in the vertical direction with 90% sensitivity. However, both cutoffs had low specificity (<45%).

On the other hand, UC and HC showed lower sensitivities compared with BMI, indicating lesser interest in predicting setup errors. Plausibly, some BMFs may have a greater effect on setup errors than others, and the differential effect may vary depending on other patient-related factors. However, as suggested by Wu et al.,[13] any eventual consensus concerned with adapting the PTV-CTV margin for obese patients should consider establishing a scoring system using multiple BMFs. However, the utility of daily cone beam CT in obese patients has been widely adopted to quantify geometric uncertainties in treatment rather than adapting PTV margins.

Additionally, cone beam CT can help evaluate possible weight loss and change in tumor size that may require treatment replanning. Therefore, daily cone beam CT may be necessary for this category of patients, but may entail longer treatment times, as well as increased cost and patient exposure to higher radiation doses, notably to adjacent organs, such as the rectum.[13] To mitigate such a risk, cone beam CT scans can be optimized by using low-dose cone beam CT scans, which provide comparable image quality, as suggested by Ordóñez-Sanz et al. who presented a simple method to develop pelvis cone beam CT imaging protocols based on patient size to reduce concomitant imaging doses.[28]

Limitations

The main limitation this study is the skewed distribution in BMI, because the majority of participants were overweight or obese, which is possibly due to a high prevalence of obesity in the target population rather than selection bias, because the authors included consecutive patients. Nevertheless, this probably affected the validity of the correlation and cutoff sensitivity (ROC curve) analyses. A BMI-stratified sampling method may provide a more accurate analysis, but may require a higher patient flow.

Conclusions

The present study demonstrated a significant contribution of BMFs, including BMI, UC, and HC, to enlarging setup errors in the translational direction among patients treated for cervical and endometrial cancers. All 3 BMFs showed a significant effect on setup errors, but BMI was more sensitive in predicting a vertical shift >0.7 cm and a lateral shift >1.0 cm, and the determined cutoff corresponds to the World Health Organization obesity threshold. In the absence of a consensus regarding the adaptation of PTV-CTV margins for obese patients, further data are required to determine the optimal frequency of image guided RT to minimize setup uncertainty in such patients. The clinical interest of daily cone beam CT in obese patients, weighed with the resulting high-radiation exposure, indicates the need to consider low-dose cone beam CT protocols in this category of patients. Additionally, further research efforts are warranted to explore the effects of different BMFs and the possibility of establishing a weighed score.

Acknowledgments

Supplementary materials

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