Original paper

Relations between dose cumulated in organs at risk and treatment based on different image-guidance strategies of cervical cancer

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ABSTRACT

Purpose: In this study, relations between dose cumulated in organs at risk and treatment based on different image guidance strategies (IG) of cervical cancer were analyzed.
Material/methods: Thirty patients with cervical cancer were subjected to analysis. The first phase of the study involved analysis of shifts resulting from the registration process and calculations of margins based on shifts data. The margin was calculated for two imaging scenarios – based on the analysis of bones and soft tissues. The margins thus obtained were used in the second phase of the study where the VMAT and IMRT treatment plans were prepared and, in consequence, analyzed in the light of the dose distribution.
Results: Using different IG implicates different margins for specified parts of the CTV. IG based on bones allows to establish margins for lymph nodes (CTV2) that are smaller than margins for the vagina/paravaginal tissues (CTV1). The opposite applies to the IG based on soft tissues, for which margins for CTV1 are smaller than for CTV2. While decreasing the margins for CTV1 reduces the doses in the bladder and rectum, doses cumulated in the bone marrow are independent of the size of the margin resulting from the type of IG used. Nevertheless, the average doses and the values of normal tissue complication probability in the bone marrow were smaller for VMAT than for IMRT.
Conclusion: The VMAT plan and image guidance based on soft tissue registration for the vagina/paravaginal tissues are recommended for radiotherapy of cervical cancer patients.

1. Introduction

Whole pelvis chemo-radiotherapy for cervical and endometrial cancer was dominant in the twentieth century, and the associated gastrointestinal, genitourinary, and hematologic toxicities resulting from these large fields have been accepted as unavoidable [1]. At the beginning of this century, a lot of clinicians tried to redefine the method of dose delivery to gynecological patients based on new radiotherapy techniques, such as intensity modulated radiation therapy (IMRT). As a result, dosimetric studies performed for IMRT for whole pelvic irradiation shows a higher conformity of the dose distribution ensuring excellent coverage of the planning target volume (PTV) by the therapeutic dose and simultaneous reduction of high doses (30 Gy dose or higher) in organs at risk (OAR), such as the bladder, rectum and bowels, for which the volumes absorbing the high doses have been reduced by more than 20% for the bladder and rectum and more than 50% for the bowels [2–4]. The usage of intensity-modulated techniques allows a

dose reduction in the bone marrow (BM) [5–7]. Studies that reported this benefit were performed for basic IMRT methods realized on conventional (C-arm) accelerators, as well as for advanced methods, such as volumetric modulated arc therapy (VMAT) and IMRT methods realized on non-conventional machines, such as tomotherapy [8–12]. Generally, the reduction of doses in BM, noted in the cited studies, were observed when the planning strategy assumed the usage of BM as an OAR during treatment plan optimization and when BM was not used as an optimization structure. The study published by Murakami et al. showed the superiority of the first strategy when BM is used as OAR during optimization [13]. Moreover, we show that for conventional accelerators, the best results of dose reduction in BM are observed for VMAT [14].

Pelvic organs are naturally prone to positional and volumetric changes over time. As a result, the pelvic anatomy at the time of radiotherapy planning may differ from the pelvic anatomy during treatment. While during the whole pelvic irradiation with three-

dimensional conformal radiation therapy (3D-CRT), the movement of the pelvic organs is not particularly important (the region of therapeutic doses cover CTV with a large margin), then, in the case of intensity-modulated techniques (e.g. IMRT, VMAT, tomotherapy), they start to play a significant role [15,16]. For successful implementation, the intensity-modulated techniques need accurate delineation of CTV and selection of an appropriate margin around the CTV to form the PTV. The CTV-PTV margin is based on the internal margin, which accounts for organ motion and the set-up margin, which accounts for patient set-up and delivery errors [17]. Appropriate determination of internal target volume (ITV) depends on the CTV movements that are independent of or induced by other organs, such as the bladder, rectum and bowels. The movements are different for specific parts of CTV, such as the gross tumor volume (GTV), cervix, uterus, upper vagina, parametrium and pelvic nodes [18]. For example, the nature of movements of the cervix or upper vagina generally depends on GTV reduction during treatment and daily-filling of the OARs (e.g. bladder, rectum) and is different from the nature of movements of the pelvic nodes which are largely dependent on the displacements of the pelvic bones that could be detected from day to day, during patient positioning. The set-up margin depends on methods of patient immobilization, scheme of geometrical verification used for patient positioning and irradiation and experience of radiation therapy technologists. For example, when the image guidance procedures are based on two-dimensional kilo-voltage images (2D-kV), then compatibility of the bony anatomy is generally verified and, in consequence, the set-up margin for parts of CTV that are independent of the bony anatomy (e.g. cervix, uterus, upper vagina) should be bigger than for parts of CTV that are dependent on bony displacements (e.g. pelvic nodes). The reverse tendency is observed for procedures using three-dimensional images (e.g. cone-beam computed tomography, CBCT). Therefore, PTV margins (set-up errors and internal motions) should be based on utilizing data from the treating institution [19].

The intensity-modulated techniques are recommended by the European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO) and European Society of Pathology (ESP) as external beam radiation therapy during the management of cervical cancer [20]. Using intensity-modulated techniques, proper selection of the PTV ensures delivery of the expected therapeutic dose to the CTV [21]. However, the doses absorbed in the OARs might depend on the shape of the PTV and the image guidance (IG) protocols. This topic is not thoroughly discussed in literature. Therefore, the authors decided to analyze the impact of the different image-guidance scenarios realized during intensity-modulated techniques on the dose cumulated in the bowels, rectum, bladder and BM.

2. Materials and methods

To analyze relations between dose cumulated in organs at risk and treatment based on different image-guidance strategies of cervical cancer, the authors (1) analyzed the registration shifts obtained separately by bone and soft tissue registrations for tomotherapy (MVCT imaging) and conventional linacs (CBCT imaging) patients, (2) confirmed that, statistically, the results for MVCT and CBCT are as similar as to allow to use tomotherapy data for image guidance on linacs, (3) proposed to use information from imaging for tomotherapy patients to calculate van Herk's margins for two imaging protocols, (4) employ these margins for planning and treatment patients on conventional linacs and, finally, (5) evaluated the planned doses to the bladder, rectum, bone marrow and (6) added NTCP calculations to find the best therapeutic solution. All steps are described in detail below.

2.1. Patient data and volume definition

The study involved retrospective data of 30 patients with cervical cancer. All patients underwent planning computed tomography (kVCT)

and received image-guided intensity-modulated radiation therapy on a tomotherapy machine (20 patients) (Accuray Inc., Sunnyvale, CA, USA) and on conventional accelerators (10 patients) (Varian Medical Systems, Palo Alto, CA, USA) between 2012 and 2015 in our hospital.

The CT scans (Definition AS, Siemens, Germany) were performed in the supine position (2 mm slice thickness) with a knee and feet support (Combifix; CIVCO Radiotherapy, Coralville, IA, USA). The clinical target volume (CTV) was defined according to the guidelines presented by Lim et al. and Small et al. and included the upper vagina, parametrial/paravaginal tissues, common, external and internal iliac lymph nodes [18,22]. If a patient had cervical cancer or endometrial cancer with cervical stromal invasion, the presacral lymph nodes were outlined. Additionally, the following OARs were delineated: rectum, bladder, femoral heads, bowels and total BM. The rectum was contoured from the anus to the sigmoid flexure. The bowels were contoured from the L4-5 interspace to its lowest extent in the pelvis as an entire bag. Total BM was contoured from the L4 vertebral body to the ischial tuberosities, including the pelvis, L4-5, and sacrum, as described by Rose et al. [23]. Total BM was delineated without specification of functional BM sub-volumes [24].

The treatment was realized in 28 fractions to deliver 50.4 Gy total dose to PTV. For patients treated on tomotherapy machine, daily megavoltage computed tomography (MVCT) was performed before the dose delivery. Image guidance scheme for patients treated on a conventional accelerator included imaging performed two times a week (usually on Tuesday and Friday) by cone-beam computed tomography (CBCT) and three times a week by two orthogonal 2D-kV images. Study involved the data of 116 CBCT images gathered from 10 patients treated on conventional accelerators and 560 MVCT images gathered from 20 patients treated on a tomotherapy machine.

2.2. Analysis of the CTV motions and method of margins computations.

Taking into account a different nature of potential movements for the treated volume, the CTV was split to CTV1 (vagina and paravaginal tissues) and to CTV2 (lymph nodes). We took initial assumptions that CTV1 movements depend on GTV reduction during treatment and daily-filling of the bladder and rectum, while the movements of CTV2 depend on the displacements of the pelvic bones that could be detected from day to day, during patient positioning. Based on these assumptions, the MVCT or CBCT scans were co-registered rigidly and automatically with the planning kVCT scans using a mutual information algorithm [25]. The automatic registration was performed in two steps, where the first one was based on the registration of the bony structures (AR^B) and the other, on the soft tissues (AR^{ST}). After each step of automatic registration, visual inspection of the accuracy of the overlap of CTV1 and CTV2 was performed. If the result of automatic registration was insufficient, the manual correction was applied, respectively, after AR^B for improvement of CTV2 alignment (MC^B) and after AR^{ST} for improvement of CTV1 alignment (MC^{ST}). While the MC^B was performed for 28% of registrations and ranged from 1 mm to 3 mm, the MC^{ST} was necessary for 72% of registrations and ranged from 1 mm to 5 mm. Due to inter-observer error, the manual corrections lower than 1 mm were not included [26]. Fig. 1 shows the scheme of the registration process and phases of shifts collecting.

The total shift corresponds to the shift that is needed to obtain an accurate alignment for CTV1 and is defined as a shift obtained during the first and second phase of registration and was analyzed for each direction separately. The formula of the total shifts in one direction is expressed as:

$$TS = S^B + S^{ST} \tag{1}$$

where: S^B is a shift from the first phase of registration based on the bony anatomy ($AR^B + MC^B$) and S^{ST} is a shift from the second phase of registration based on soft tissues ($AR^{ST} + MC^{ST}$).

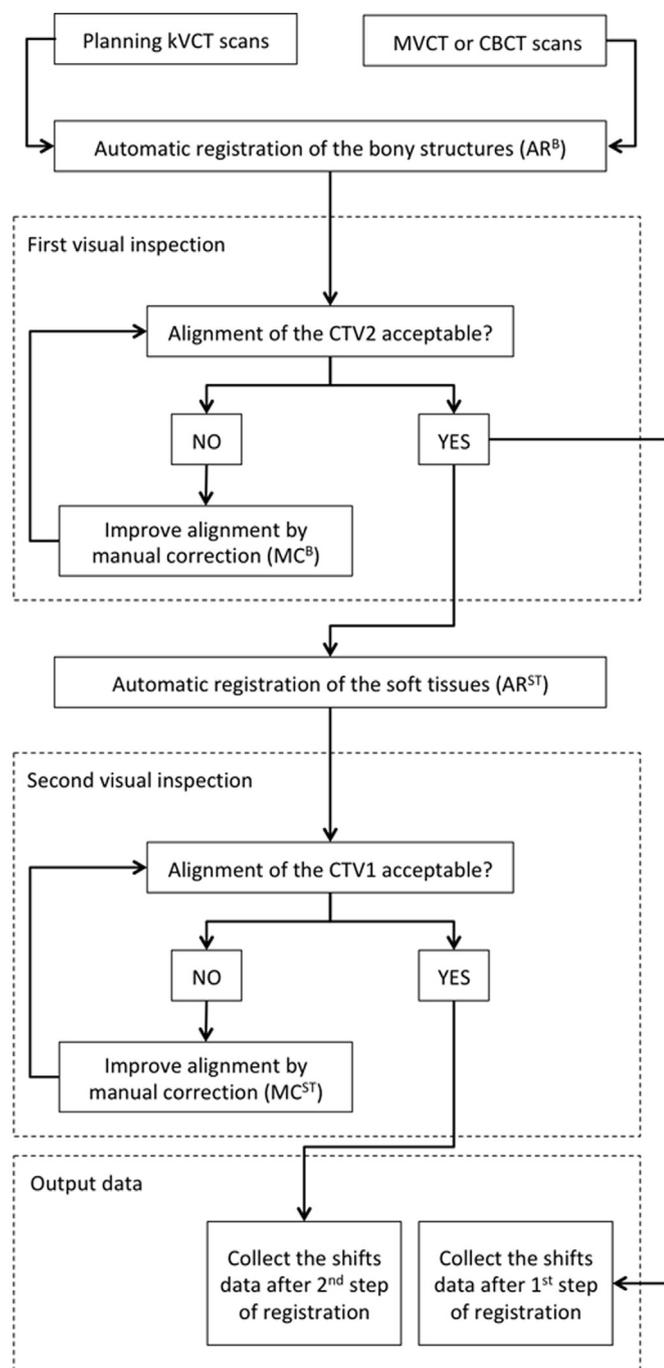The components of total shifts in three directions (x, y, and z axes)

Fig. 1. Scheme of the registration process and shifts collecting. Meaning of abbreviations used: kVCT scans – the scans obtained from diagnostic computer tomography; MVCT scans – the scans obtained on the tomotherapy machine; CBCT scans – the scans obtained on the conventional accelerator; CTV1 – clinical target volume including the vagina and paravaginal tissues; CTV2 – clinical target volume including the lymph nodes.

were analyzed separately. Moreover, they were collected separately for the patients treated on conventional (CBCT used for registration) and tomotherapy (MVCT used for registration) machines. To confirm similarity for these groups, statistical testing, including verification of normality of distribution (Shapiro-Wilk test), statistical dispersion (Kolmogorov-Smirnov test) and central tendency (Mann-Whitney U test), were performed at the significance level $\alpha = 0.05$ and statistical power of 0.8 [27,28]. During analysis of these data, we confirmed the normality of distribution for each group of the shifts used for computations of average shifts (p-values were higher than 0.3 for each group).

Analysis between shifts obtained for CBCT and MVCT (separately for each of directions) confirmed for them the homogeneity of the variances (p-values higher than 0.09 for each group) and the absence of statistical differences between averages (p-values higher than 0.05 for each group) (Table 1). These results allow us to use the margins computed on MVCT for treatment plans preparation for conventional accelerators.

The shifts data from tomotherapy machine were used for margin calculation for two different IG protocols: IG-ST simulating the scheme when a limited number of sessions based on registration of the CTV1 was used and IG-B simulating the scheme when a limited number of sessions based on registration of bony anatomy (with movements corresponding to the movements of the CTV2) was used (Fig. 2).

For IG-ST protocol, we assumed that IG focused on CTV1 and was performed only for the first five fractions ($k = 5$). The average of the TS from the first five fractions (aTS) was considered as a correction to be applied to subsequent treatment fractions when IG was discontinued. For each next fraction starting from the 6th one and ending on 28th one, the difference between TS and aTS determines the residual fraction error (RE) that is connected with the position of the CTV1 [29,30]. The movement of the CTV1 differs from the movement of CTV2, so RE for CTV2 was calculated as the difference between TS and S^{ST}. IG-B protocol assumed that IG focused on registration of the bony anatomy (S^B) strictly connected with CTV2. The correction margin was calculated from the first five fractions of the average of the S^B (aS^B). As a result, the RE for CTV2 in this protocol was calculated as the difference between S^B and aS^B while the RE for CTV1 was the difference between TS and S^B.

The treatment margins required to encompass residual setup errors for CTV1 and CTV2 and for each simulated IG protocol were calculated using the van Herk formula ($2.5\Sigma + 0.7\sigma$), a well-known population-based method of determining the margin that could ensure a minimum of 95% dose coverage for 90% of patients [31]. The systematic population error (Σ) was defined as an indication of the spread of individual mean residual errors. It is calculated as the standard deviation (SD) of the distribution of mean residual errors for each individual patient. The random population error (σ) was calculated as the mean of individual random errors. Individual random errors for each patient from the population were defined as the standard deviation (SD) of the measured residual errors over the course of treatment and quantified the spread of residual errors [17].

2.3. Treatment plan preparation and analysis of dose distribution.

The treatment plans were prepared for Varian TrueBeam™ accelerator (Varian Medical Systems, Palo Alto, CA, USA) using Eclipse™ treatment planning system ver. 13.6 (Varian Medical Systems, Palo Alto, CA, USA). The analytic anisotropic algorithm with the spatial resolution of 2.5 mm was used for computing dose to the irradiated region. Respectively, for each of 30 patients, X6MV 7-field IMRT and 2-arc VMAT treatment plans for two sets of margins calculated on the basis of two different schemes of IG-protocols (IG-ST and IG-B) were prepared. External beam dose was 50.4 Gy delivered in 28 daily fractions.

The plans were optimized using constraints similar to the RTOG 0418 trial the volume of small bowel receiving > 40 Gy was limited to < 30%, < 60% of the rectum was to receive > 30 Gy, and < 35% of the bladder was to receive > 45 Gy [32]. In addition, we used two-step optimization for the distribution of doses in the BM. Firstly, according to the study presented by Albuquerque et al., we tried to reduce the volume of the BM receiving doses > 20 Gy to the volume of < 80% of the whole pelvic BM and, secondly, we tried to reduce the dose in this structure as much as possible [5]. For each plan, ICRU-83 plan normalization criteria were followed, with prescription to the median dose on PTV [33].

The dose distributions in BM obtained by IMRT and VMAT plans were compared for IG-ST and IG-B margins. The qualitative analysis of

Table 1
The averages and standard deviations (in brackets) of the total shifts and their components – shifts based on the bony anatomy registration correspond to the CTV2 alignment and shifts based on soft tissue registration correspond to the CTV1 alignment. Data collected for each direction and for two methods of imaging.

Direction	Method of Imaging	Average Shift (SD) [mm]			p-values from statistical testing of Total Shifts		
		Bony Anatomy	Soft Tissues	Total Shifts	Normality	Homogeneity	U test
Superior/Inferior	CBCT	−0.1 (6.1)	0.3 (2.3)	0.1 (6.2)	p = 0.712	p = 0.094	p = 0.059
	MVCT	0.2 (5.8)	0.1 (2.6)	0.1 (5.9)	p = 0.339		
Anterior/Posterior	CBCT	0.2 (6.3)	−0.1 (3.4)	0.1 (6.9)	p = 0.627	p = 0.164	p = 0.172
	MVCT	0.1 (6.5)	−0.3 (3.7)	−0.1 (7.1)	p = 0.843		
Left/Right	CBCT	−0.2 (5.4)	0.1 (1.2)	0.0 (5.2)	p = 0.533	p = 0.112	p = 0.121
	MVCT	0.0 (5.2)	−0.2 (1.4)	−0.1 (4.9)	p = 0.613		

Bony Anatomy – shifts correspond to CTV2 (lymph nodes) alignment.
Soft Tissues – shifts correspond to CTV1 (vagina and paravaginal tissues) alignment.
CBCT – cone beam computed tomography, images performed on conventional accelerators.
MVCT – mega voltage computed tomography, images performed on tomotherapy.

the obtained doses in relation to the doses specified during optimizations was performed. The evaluation of dose in BM was performed in the light of doses cumulated in PTVs and other OARs (bladder, rectum and bowels).

Based on obtained dose distributions, modeling of the normal tissue complication probability (NTCP) for BM was performed. The Lyman-Kutcher-Burman-NTCP (LKB-NTCP) [34] with Bazan's method [35] was implemented. LKB-NTCP formula is expressed as:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} exp\left(-\frac{x^2}{2}\right)dx \qquad (2)$$

$$t = \frac{D - TD_{50}}{m \cdot TD_{50}} \qquad (3)$$

$$TD_{50}(\upsilon) = TD_{50}(1) \cdot \upsilon^{-n} \qquad (4)$$

$$\upsilon = \frac{V}{V_{ref}} \qquad (5)$$

where: D is the uniform dose calculated by the generalized equivalent uniform dose formula proposed by Niemierko [36]; TD50 is the tolerance dose for a 50% complication probability for uniform doses to the BM; m is a dimensionless parameter to determine the slope of the complication probability according to dose curve; n is the parameter for the volume dependence of the complication probability and Vref is a reference volume for the BM. The values of n = 1, m = 0.27 and TD50 = 35 Gy were taken for computations from Bazan's study [35].

The statistical analyses of the differences between average doses as well as NTCP values were performed by Friedman ANOVA with Nemenyi's procedures used as post-hoc tests. All tests were performed on the significance level equal to 0.05.

3. Results

3.1. The CTV motions and computed margins

Table 2 shows systematic (Σ) and random (σ) errors and population-based margins calculated for every combination of the referencing volume (CTV1 or CTV2) and IG protocol (IG-ST or IG-B, Fig. 2).

Margins computed according to the first image guidance protocol (IG-ST) were smaller for CTV1 than for CTV2 and were 8 mm (for CTV1) and 12 mm (for CTV2) for the inferior/superior and anterior/posterior directions and 6 mm (for CTV1) and 10 mm (for CTV2) for the left/right direction. A reverse relationship was observed for the IG-B protocol where margins were 13 mm (for CTV1) and 7 mm (for CTV2) for the inferior/superior and anterior/posterior directions and 11 mm (for CTV1) and 6 mm (for CTV2) for the left/right direction.

3.2. Analysis of dose distribution

The dose distributions were analyzed for 120 treatment plans prepared for 30 patients: four possible combinations for two radiation therapy techniques (IMRT and VMAT) and two different sets of PTV-CTV (IG-ST and IG-B) (Table 2). Each prepared plan met the constraints used during the optimization process. Table 3 shows mean dose obtained from 30 patients in a specified part of structures that was collected for four possible scenarios of treatment proposed in this study. IG-ST and IG-B protocols noted in Table 3 correspond to margins in the superior/inferior, anterior/posterior, left/right directions that were calculated separately for CTV1 and CTV2 (Table 2).

Analyzing the data in Table 3, we found that, the mean doses in each evaluation point of PTV were similar (the differences were not statistically significant, p > 0.2 for each evaluation point). The statistically significant differences were observed for the evaluation points in the bladder and rectum. Plans based on different sets of margins (IG-ST or IG-B) differ in collected doses (for IG-B the doses are higher than for IG-ST, p < 0.008), while the doses in the plans prepared in two different techniques (IMRT or VMAT) were not statistically different (p > 0.131). Analysis of doses in the bowels and BM, showed noticeable higher doses deposited in 30% (bowels) and 80% (BM) of the volume of these structures for IG-ST protocol than for IG-B, but these differences were not statistically significant (p > 0.1, for each evaluation). Additionally, the different techniques (IMRT or VMAT) do not lead to statistically significant differences between doses deposited in 30% (bowels) and 80% (BM) of the volume of these structures (p > 0.1, for each evaluation). To find additional information about the dose distribution in BM, the analysis of the average doses deposited in this structure was performed. Average dose in BM was calculated from the mean doses obtained in BM for each patient separately. Average doses and their standard deviations (in brackets) for BM were, respectively: 28.9(1.3) Gy for IMRT(IG-ST), 27.4(1.5) Gy for IMRT(IG-B), 26.7(1.1) Gy for VMAT(IG-ST) and 25.8(1.6) Gy for VMAT(IG-B). Statistically significant difference was found between average doses in BM deposited through VMAT(IG-B) and IMRT(IG-ST) schemes (p < 0.02). Although the average doses in BM for IMRT(IG-B) and VMAT(IG-ST) were higher than those for VMAT(IG-B), statistically significant differences were not confirmed.

Fig. 3 shows relations between the NTCP values and analyzed schemes of irradiation. The NTCP values and their standard deviations (in brackets) were, respectively: 0.243(0.059) for IMRT(IG-ST), 0.211(0.053) for IMRT(IG-B), 0.141(0.055) for VMAT(IG-ST) and 0.089(0.049) for VMAT(IG-B). The NTCP values obtained for IMRT(IG-ST) and for IMRT(IG-B) were significantly higher than for VMAT(IG-B) (p < 0.004 for each comparison). We did not find significant differences between the NTCP values obtained for VMAT(IG-ST) and VMAT(IG-B).
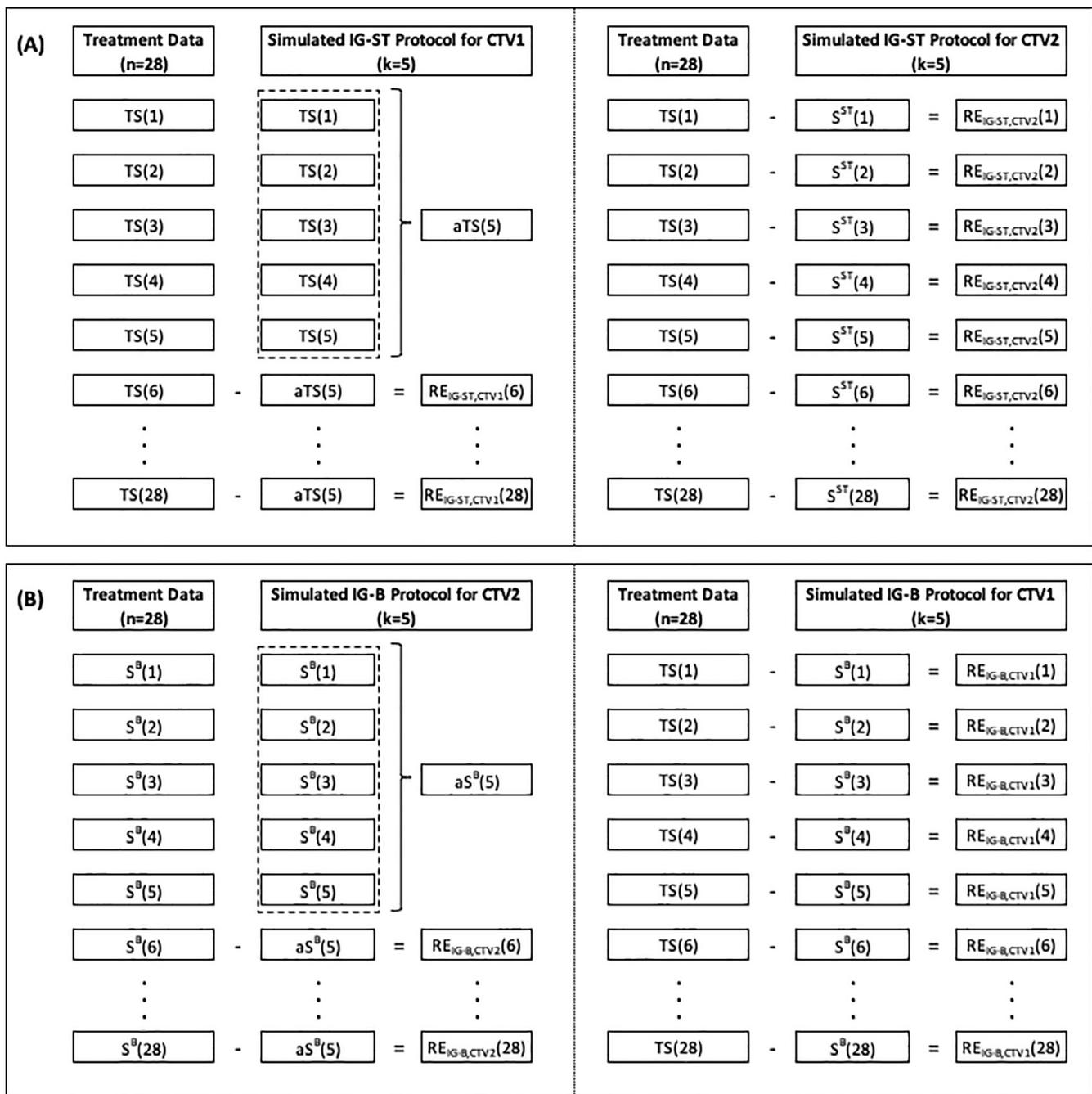
Fig. 2. Schemes of the image guidance (IG) protocols used in the study: (A) IG-ST, (B) IG-B which were based on the referencing scenario including the first five fractions as a reference. Meaning of abbreviations used: n – number of fractions; k – number of initial fractions used as a reference; TS – total shift; S^B – shift from the first phase of registration based on the bony anatomy; S^{ST} – shift from the second phase of registration based on soft tissues; RE – residual errors; aTS – average of the total shifts collected during the first five fractions; aS^B – average of the shifts from first phase of registration based on the bony anatomy collected during the first five fractions; CTV1 – clinical target volume including the vagina and paravaginal tissues; CTV2 – clinical target volume including the lymph nodes.

4. Discussion

The intensity-modulated techniques, such as IMRT or VMAT, are recommended by major European organizations (ESGO, ESTRO and ESP) as external beam radiation therapy during management of cervical cancer [20]. One of the most important parts in the preparation of intensity-modulated techniques is the optimization process, during which the dose distribution is optimized in the target volume and organs at risk. While the volumes of the bladder, rectum and bowels are normally used during optimization, the usage of BM was not obvious. Our previous study shows that the use of BM during optimization of the fixed-

beams IMRT and VMAT plans effectively reduced the dose in BM without increasing the dose in the bladder, rectum and bowels [14]. One of the key issues that has not been analysed in our previous study and is the main scope of this analysis concerns the impact of different IG strategies on the dose cumulated in the BM and other OARs.

4.1. CTV motions and computed margins

Image-guided radiation therapy (IGRT), with its many aspects, including patient set-up, margin value and pre-treatment imaging, aims to reduce geometric uncertainty. At a time when IMRT for cervical

Table 2
Systematic (Σ) and random (σ) errors and population-based margins in millimetres calculated for each combination of the image guidance (IG-ST or IG-B, see Fig. 2) protocol and referencing volume (CTV1 or CTV2).

Direction	Errors and Margins [mm]	IG-ST		IG-B	
		CTV1	CTV2	CTV1	CTV2
Superior/Inferior	Σ	1.9	3.4	3.6	1.5
	σ	3.6	4.1	4.7	3.5
	Margin	7.3	11.4	12.3	6.2
Anterior/Posterior	Σ	2.0	3.8	3.9	1.7
	σ	4.2	3.6	4.6	3.5
	Margin	7.9	12.0	13.0	6.7
Left/Right	Σ	1.5	2.9	3.1	1.6
	σ	2.8	3.7	4.2	2.7
	Margin	5.7	9.8	10.7	5.9

cancer is being adopted, the most reproducible and clinically practical IGRT methods must be determined. In our study, two different image guidance scenarios were developed and evaluated. These scenarios correspond to the two most common strategies for the control of patients during radiotherapy, when alignment is based on soft tissues (IG-ST) and when alignment is based on rigid structures (bones) whose movements strictly correspond to the movement of the pelvis lymph nodes (IG-B). Both of these scenarios are based on translation-only method for patient setup.

Our analyses confirmed the similarity of the total shifts and their components (shifts based on bony anatomy and soft tissues) for the patients treated on the conventional accelerator and tomotherapy machine. We confirmed normality of distribution and similarity of dispersion and central tendency between these data. Statistical test used for analysis of central tendency (Mann-Whitney *U* test) requires similarity of the size of compared groups. Specifically, the maximal accepted disproportion between the size of groups should be equal to 1:2 [27]. In our study we gathered 110 CBCT and 560 MVCT observations. Therefore, to allow analysis of the central tendency, the MVCT group was randomly resampled to the same number of observations as that collected for the CBCT group. The compatibility obtained between MVCT and CBCT groups has enabled us to calculate the margins for the group of patients treated on the tomotherapy machine and, in the next step, application of these margins for patients treated on the conventional accelerator.

The differences between the margins obtained for the two image guidance strategies were characterized by a noticeable regularity. As shown in this study, IG procedures based on control of the vagina and paravaginal tissues (CTV1) (IG-ST) allow to use relatively small margins
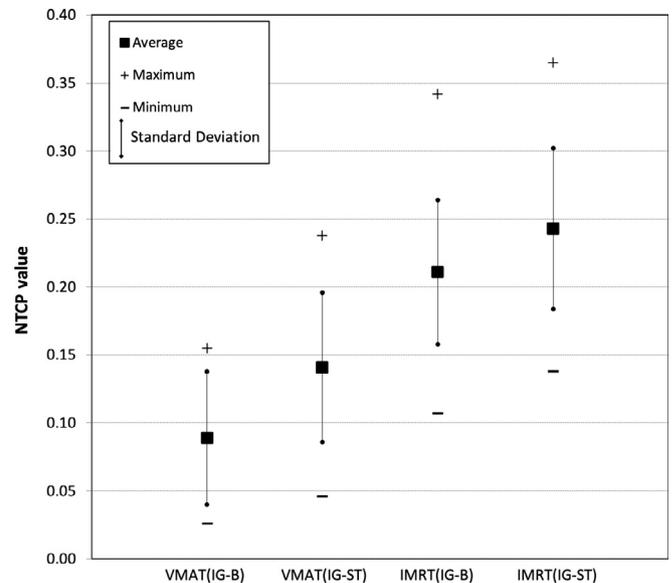

Fig. 3. Relations between the normal tissue complication probability (NTCP) values and four planning scenarios: IMRT and VMAT – intensity modulated radiation therapy and volumetric modulated arc therapy prepared for two sets of margins obtained from different image guidance protocols (IG-ST and IG-B).

for CTV1 (range, depending on the direction, from 6 to 8 mm) and bigger margins for lymph nodes (CTV2) (range, depending on the direction, from 10 mm to 12 mm) (Table 2). The opposite is noted for IG procedures based on control of the bony anatomy (IG-B) that allow us to reduce margins for CTV2 (range, depending on the direction, from 6 mm to 7 mm) and require bigger margins for CTV1 (range, depending on the direction, from 11 mm to 13 mm) (Table 2). Obtained margins reflect the different nature of CTV2 and CTV1 mobility and confirm that by using selected image guidance protocol we could focus on a better control of the position of only one of the CTVs while increasing the uncertainty of the position of the other CTV.

General implications of our analysis of the shifts and the margin calculations are compatible with the literature data. Jadon et al. summarized where the movement of specific parts of the CTV during radiation therapy of gynecological cancer in a review study [21]. Both in our study and in Jadon's review, greater cervical motion in the anteroposterior and superioreinferior directions, with less seen laterally, was noted. The movement of the lymph nodes (CTV2 – in our study) was analyzed only in two papers [37,38]. Unfortunately, the results presented in these works were not associated with various image

Table 3
Mean dose in a specified part of structure obtained during the optimization process for four planning scenarios: IMRT and VMAT – intensity modulated radiation therapy and volumetric modulated arc therapy prepared for two sets of margins obtained from different image guidance protocols (IG-ST and IG-B). Optimization process was performed according to the constraints of the dose distribution related to specific structures and recommended by ICRU-83, RTOG 0418 trial and Albuquerque et al. (25–27).

Structure (% of Volume)	Optimization Constraint [Gy]	IMRT(IG-ST)	IMRT(IG-B)	VMAT(IG-ST)	VMAT(IG-B)	Statistical comment
		Mean Dose in specified part of volume [Gy]				
PTV (98%)	≥ 45.4	45.5	45.7	46.9	46.6	
PTV (95%)	≥ 47.9	48.4	48.7	49.1	48.9	Statistically similar. $p > 0.2$ for each evaluation point.
PTV (50%)	~ 50.4	50.4	50.4	50.4	50.4	(Friedman ANOVA)
PTV (2%)	≤ 53.9	53.4	53.2	53.8	53.6	
Bladder (35%)	< 45.0	40.7	44.2	38.2	43.8	Statistical difference between doses grouped by IG protocols
Rectum (60%)	< 30.0	27.1	29.8	26.6	28.9	(IG-ST vs IG-B). $p < 0.001$ (Friedman ANOVA) $p < 0.008$ (post-hoc tests)
Bowel (30%)	< 40.0	37.4	36.9	37.9	37.5	Statistically similar.
BM (80%)	< 20.0	16.6	15.7	16.3	15.2	$p > 0.1$ for each evaluation point. (Friedman ANOVA)

PTV – planning target volume including CTV1 and CTV2 with correspond margins.
BM – bone marrow.

guidance schemes. Therefore, our study complements the published studies.

4.2. Analysis of dose distribution

Tumor and OARs movement, deformation, and change in volume can be substantial during the course of fractionated intensity modulated techniques of radiation therapy for cervical cancer. Adequate image guidance process allows us to add sophisticated margins that are generally smaller than margins used without imaging control and it leads to dose reduction in the bladder, rectum and bowels and reduced toxicity of the radiation therapy in these organs [18,39]. The effect of dose reduction in the BM depending on applied margins was not fully analyzed. Potential benefits of dose reduction in the BM through the use of intensity-modulated techniques have so far been analyzed without taking into account the differences between the PTV-CTV margins depending on the schemes of image guidance [5–14]. Based on our results on the size of the margins, it can be assumed that for the IG-ST protocol, a smaller margin for CTV1 should allow smaller doses in the bladder, rectum and bowels than the margin for CTV1 applied on the basis of IG-B and the doses in the BM should be higher for IG-ST than for IG-B, because the margin for CTV2 calculated for IG-ST is bigger than the one for CTV2 for IG-B (Table 2). To check this hypothesis, we performed analysis of dose distribution for patients for whom VMAT and IMRT plans were simulated for two different sets of margins calculated on IG-ST and IG-B protocols. Based on our previous study, we decided to include in current analysis only the planning strategy including the optimization of the dose in BM, for which higher benefit in dose reduction in BM was noted than for the strategy without the optimization of the doses in BM [14].

Simulated treatment plans met the guidelines for expected dose distributions (Table 3). Moreover, we confirmed that for the scheme with a smaller margin for the vagina and paravaginal tissues (CTV1) (IG-ST), lower doses in the bladder and rectum were deposited than for the IG-B scheme (bigger margin for CTV1). No differences for dose distribution in the bladder and rectum obtained from IMRT and VMAT techniques were noted. Based on this analysis, the dose distributions in the bowels and BM were similar and independent of the IG scheme or technique of radiation therapy (Table 3). However, analysis of the average dose and of the NTCP value for BM showed superiority of VMAT plans to IMRT plans.

Finally, the best solution was the VMAT plans realized in the IG-ST scheme (VMAT(IG-ST)) because the IG-ST scheme allows the reduction of doses in the bladder and rectum (caused by smaller margin for CTV1) and VMAT plans allow to obtain better dose distributions in BM. From the perspective of BM, the important information is that IG protocols (different margins, especially for CTV2) do not affect the doses cumulated in BM.

5. Conclusion

Using different image guidance protocols implicates different margins for specified parts of CTV during radiation therapy of cervical cancer. Protocols based on the bony anatomy allow to establish margins for lymph nodes (CTV2) that are smaller than margins for the vagina and paravaginal tissues (CTV1). The opposite applies to the protocols based on soft tissues, for which margins for CTV1 are smaller than for CTV2. While decreasing the margins for CTV1 reduces the doses in the bladder and rectum, doses cumulated in the bone marrow are independent of the size of the margin resulting from the type of image guidance protocol used. The average doses and the values of normal tissue complication probability in the bone marrow were smaller for VMAT than for IMRT. VMAT plans supported by image guidance protocols based on soft tissue are recommended for radiation therapy of cervical cancer.

Conflict of interest

None

Acknowledgement

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