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Review

Problems and solutions in IGRT for cervical cancer

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ABSTRACT

The contribution of Image-guided Radiotherapy (IGRT) to modern radiotherapy is undeniable, being the way to bring into daily practice the dosimetric benefits of Intensity-Modulated Radiotherapy (IMRT). Organ and target motion is constant and unpredictable at the pelvis, thus posing a challenge to the safe execution of IMRT. There are potential benefits of IMRT in the radical treatment of cervical cancer patients, both in terms of dose escalation and decrease of toxicity. But it is essential to find IGRT solutions to control the aspects that can lead to geographic miss targeting or organs at risk (OAR) overdose. This review seeks to describe the problems and possible solutions in the clinical implementation of IMRT/IGRT protocols to treat intact cervical cancer patients.

1. Background

Cervical cancer is a common cause of consultation in Radiotherapy and Oncology facilities around the world. According to Global Cancer Observatory 2012, it is the fourth leading cause of cancer in women with an annual incidence of 527,000 cases and 265,000 deaths.[1] Most patients with cervical cancer are young women under 50 years of age that are diagnosed at a locally advanced stage.[2,3] Nowadays, a concomitant treatment of radiotherapy/chemotherapy is considered the standard treatment for cervical cancer, due to its effectiveness in terms of local control and survival rate. Nonetheless, there are still many challenges to face for this type of approach, specifically in the radiotherapy field. Hence, cutting-edge research in radiotherapy focuses on the potential of radiation to effectively deal with this disease.

Intensity-Modulated Radiotherapy (IMRT) is a technique able to achive better conformity and dose distribution than 3D conformal techniques. These characteristics make it an ideal approach to reduce organs at risk (OAR) exposition improving toxicity outcomes, or to intensify doses at target to improve local control.[4,5] However, there is still some uncertainty as to its reproducibility on a daily basis and how it could affect clinical results.

Targets and organs motion are the enemies to beat in implementing IMRT as a standard treatment in cervical cancer patients. Pelvic anatomy is complex and comprises several organs and structures with unpredictable and non-orchestrated movements. Additionally, in order to obtain the best oncological results, volumes to treat have to involve not only the macroscopic tumor and cervix, but also the uterus, parametrial tissue, vaginal-paravaginal tissue and lymph node regions at risk. All these together pose a challenge to get a reasonable safety margins, enough to cover the tar-

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get and its variations, but not too large as otherwise IMRT advantages could be lost.

Image-guided Radiotherapy (IGRT) is an indispensable tool to control/minimize the treatment uncertainties and reduce the risks of target miss and/or OAR overdose during radiotherapy delivery. Defined as three-dimensional follow-up with imaging before, during and/or after radiotherapy administration,[6] it is at this time the way to bring to daily practice the dosimetric benefits of IMRT. For pelvic radiotherapy, the contributions are huge and it is becoming a requisite to subject patients to this technique. There are many IGRT systems in the market, each with a different guidance solution, but all are able to perform 3D following and not just 2D verification. Thus, choosing one or another depends on facility experiences, needs and resources. Perhaps, the most widely used and growing IGRT option in clinics is the cone beam computed tomography or CBCT. This is an in-room tomography imaging employing kilovoltage X-rays capable of showing not only bone or fiducial markers but also soft tissue, and carrying out a comparison on-line/on-site between acquired images and tomography images used for planning.

This review seeks to describe the problems and the possible solutions in the clinical implementation of IMRT/IGRT protocols to treat intact cervical cancer patients.

2. Problem description

The accuracy of IMRT delivery is affected by volume contouring, set-up errors and inter-/intra-fraction organ movements and deformation. Although all these aspects are important, the most relevant in cervical cancer is target and organ motion. The pelvic organs move continuously for many reasons mainly because of variations in the bladder and rectum filling (Fig. 1, DICOM files). These changes may result in variations in the clinical target volume, so the selection of appropriate contours and margins is mandatory.

Guidelines have been developed for delineation in cervix cancer in an attempt to unify the target volumes. In addition to gross tumor volume (GTV), the volumes to treat should include areas at risk. Thus, the components of clinical target volume (CTV) include the GTV, cervix, uterus, upper vagina, parametrial tissue and relevant draining nodal groups (common, internal and external iliac, obturator, presacral and para-aortic lymph nodes if affected).[7]

After defining CTVs, we must set up an internal target volume (ITV) as a margin to CTV that includes the variation for organs and target movements. Defining the CTV motion is a complex task. Three events are decisive and should be known to find the ideal ITV: 1. Target motion, 2. OAR variation, and 3. reduction in tumor volume and shape deformation.

2.1. *ITV considerations*

2.1.1. *Target motion*

Cervix: Knowing the tumor and cervix motion and shrinkage is essential to avoid geographic miss and/or OAR overdose during radiotherapy. Several authors have used different tools to measure cervical movement, mainly images during treatment and fiducial markers. In 2004, Lee et al. analyzed the changes in the position of the cervix implanting a sleeve and following it through portal images. The medial-lateral (ML), superior–inferior (SI) and anterior-posterior (AP) displacements were 10, 8 and 16 mm, respectively, with maximum position change of 24, 36, and 23 mm, respectively.[8] Another report came from Chan et al. in 2008 who performed a comparison of pre-determined points-of-interest in serial magnetic resonance images (MRI). In that study, the movement of the external cervix oscillated between 10 and 15 mm, suggesting that daily images should be used to capitalize the benefits of high-precision radiation in patients with cervical cancer.[9] Also Jadon et al. systematic review reported greater cervical movement in the AP and SI directions, with less ML displacement. The means of motion in this review varied from 2.3 to 16 mm in the AP 2.7 to 8 mm in the SI and 0.3 to 10 mm in the ML directions.[10] A more recent analysis was presented by Langerac et al. After implanting fiducial markers in fornix, they compared the planning CT and the daily CBCTs searching for variations, mean shifts of 0.4 mm, 1.0 mm and −3.9 mm for the ML, AP, and SI directions were found, respectively. An additional comparison between the first CBCT scan and the daily CBCTs was made, mean shifts were 0.8, 0.6 and −1.3 mm in ML, AP, and SI directions, respectively.[11] These degrees of movements must be taken into account to define optimal margins, since close margins can produce under-dosing of GTV/CTV or, in contrary, over-dosing of OAR if larger margins are used.[12]

Lim et al. postulated that a possible reason for cervix movement is the variation in the uterus position during the treatment because of the tumor regression.[13] This helps to understand the movement of the cervix after 2–3 weeks of treatment, but does not explain the changes that occur daily (interfraction motion) or during the treatment session (intrafraction motion). An explanation for both-inter and intra-fraction motion – has been offered by several authors: a direct correlation between the changes in the filling volumes of the rectum and the bladder and the position and motion of the cervix.[9,10,14,15] A description of this phenomenon is offered below.

Although interfraction motion is more relevant and larger, a range of intrafraction motions has been also reported. Yamamoto et al. reported their experiences using real-time tumor tracking with fluoroscopy to measure intrafraction movements of the cervix showing ranges from 1.4 to 4.2 mm. That is not insignificant and should also be considered in the choice of margins. In fact, margins of 5 mm at the body and 4 mm at the cervix have been proposed to encompass 95% of the intrafraction motion.[16]

Uterus: Uterine motion is probably the most unpredictable factor in pelvic radiotherapy. It can change completely in all directions – rotation included – with also changes in shape and size. This motion is not normally correlated with the displacement of the cervix and is almost always influenced by changes in bladder volume. In 2008 Taylor et al. assessed interfractional uterine motions in gynecological cancer patients, comparing 2 sets of MRI performed in two consecutive days. Differences in the position of the uterine body of 7 mm (±9.0) in the AP direction, 7.1 mm (±6.8) SI and 0.8 mm (±1.3) ML were found, indicating that large movements of the uterus may occur, particularly in the SI and AP directions.[17] In 2010

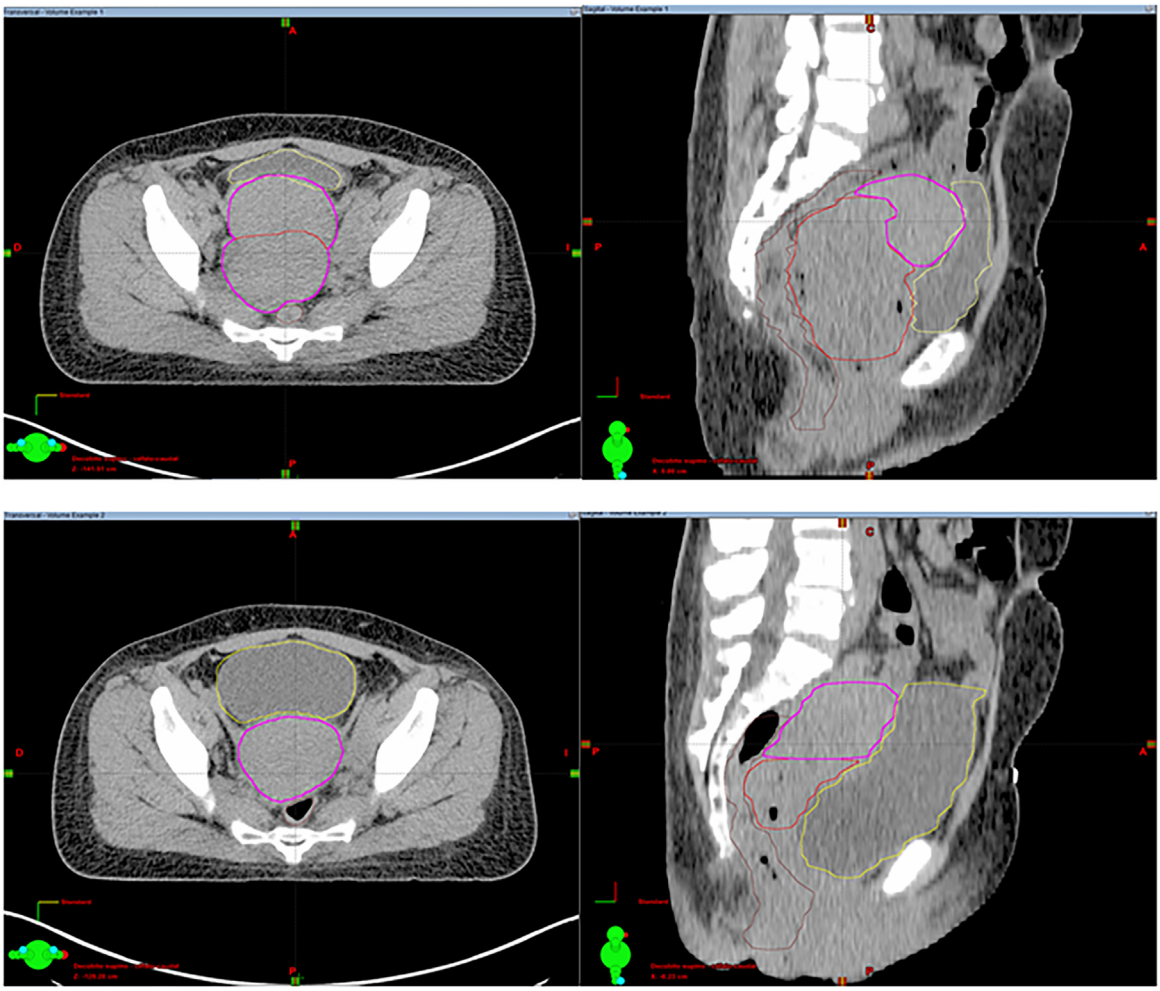

Fig. 1 – Changes on uterine and cervix position with bladder filling (uterus in magenta; GTV and cervix in red; bladder in yellow; rectum in brown). The first figure shows the uterine and cervical position at planning, with a bladder volume of 122 ml. The second figure shows adaptive planning of the same patient. A reduction in tumor size and a change in bladder volume (420 ml) is shown. The uterine position has moved both inferiorly and posteriorly significally.

Collen et al. observed through megavoltage computed tomography (MVCT) that uterine deviations in all directions were greater compared to those of the cervix. During treatment, this movement was limited to mean shifts of 3.3 ± 11.9 mm for the anterior direction, 0.3 ± 11.7 mm for the posterior direction, 0.7 ± 8.1 mm for the left lateral direction, -0.6 ± 7.5 mm for the right lateral direction, 6.1 ± 11.6 mm for the superior direction and 5.0 ± 11.2 mm for the inferior direction.[18] Maemoto et al. also determined the predictive factors affecting uterine movement during definitive radiotherapy (RT), they compared interfraction uterine movement using pre-RT planning CT ($n = 38$) and intratreatment CBCT ($n = 315$). The mean corpus movement was: superior margin (SI direction), 7.6 ± 5.9 mm; anterior margin (AP direction), 8.3 ± 6.3 mm; left margin (ML direction), 3.3 ± 2.9 mm; and right margin (ML direction), 3.0 ± 2.3 mm. They also observed a significant correlation between changes in bladder volume and the movement of the superior margin of the corpus ($\rho = 0.364$, $P < 0.001$). Additionally, there was a significant difference in movement of the superior margin of the corpus between the subgroups with and without a history of previous pelvic surgery (not related with cervical cancer) ($P = 0.007$). They concluded that changes in bladder volume and a history of previous surgery were significantly related to intrafractional corpus movement.[19] Other authors also highlighted the filling volume of the bladder as the principal cause of altering the position of the uterus, especially in the AP and SI directions. With variable bladder filling, ranges of uterus motion goes to of 5–40 mm in the SI and 0–65 mm in AP directions.[10,17,18]

A notorious aspect in uterus movement is the extreme displacement of the fundus and the rotations of the uterus angle. Fundus moves up to a maximum of 48 mm in the AP direction in some series and is the part of the uterus with the largest movements. Uterine rotation was reported up to 91° and in some patients the uterus can turn from anteverted to retroverted during the treatment, especially in patients under 60 years of age.[17]

Lymph nodes: Lymph nodes contract and change position in an important range. Reports evaluating ganglion movements had been made. A median of translations oscillating between 7 and 30 mm have been found, suggesting inhomogeneous margins of 5–9 mm to cover 95% of the volumes.[10,20] Schippers et al. measured the contraction of the pelvic and para-aortic nodes using MRI. During treatment weeks 1–3, nodal volumes increased, compared with pre-treatment scans, but in week 4 almost all the nodes had regressed by 58% on average.[21]

2.1.2. *Organs at risk variations*

Preservation of organs at risk (OAR) is the priority in radiotherapy treatments and is the principal reasons to use highly conformal treatments like IMRT. The dosimetric benefits for the small intestine, bladder, rectum, and bone marrow in cervical cancer treatments are big, but the non-orchestrated motion of all these organs makes clinical execution difficult.[12]

Bladder: The bladder undergoes continuous changes during treatment which affects the organ itself as well as the target volume and/or other organs. In 2009, Beadle et al. observed that normal variations in bladder volume could have a profound influence on the location of the cervical target. Comparisons between full-bladder and empty-bladder scans obtained on the same day showed variations in cervix perimeters up to 1.5 cm.[22] Subsequent reviews have shown that filling the bladder has less impact on the movement of the cervix than uterus. Variability in bladder filling was measured by Taylor et al. who found that if volume varies less than 50 ml, the average uterine motion is 4.2 mm, compared with 11.2 mm if variation is larger than 50 ml.[17]

The relationship between the filling of the bladder and the position of the small intestine is frequently seen in clinics. Large bladder volumes displace the small intestine out of the targets causing a reduction in its irradiated tissue. A reduction of about 83 ml (range 0–292 ml) of small intestine was observed by Georg et al. for doses of 50 Gy and 51 ml (range 0–172 ml) for doses of 45 Gy.[15]

When comparing average bladder volumes during the first five sessions with those of the last five sessions significant differences are seen. An important reduction in bladder capacity has been reported, possibly explained by the onset of radiation cystitis. The average bladder volume in the first week was 156 cc vs. 88 cc in the last week of treatment; the reduction in bladder capacity impact the uterus motion producing an average motion at the uterine fundus of 18 mm, at the uterine canal 8 mm, and at cervix of 3 mm for every 10 ml decrease.[10,18] Eminowicz et al. also reported data about changes in bladder filling. They analyzed 10 cases of cervical cancer, finding that the volume of the bladder during radiotherapy was between 45 and 578 ml, while at the planning it was larger, between 73 and 664 cm^3. The volume of the bladder increased 4 ml/min with the waiting time, decreased on average 4 ml/day during the treatment and was higher (50 ml) along the chemotherapy period. If the difference in volume is greater than 130 ml, the probability that the PTV cover the CTV is reduced by 1.9%. Additionally, if the bladder has a volume higher than 300 ml, it is not possible to reproduce it during the treatment.[23]

Rectum: Changes in rectal volume have a significant relation with the displacement of target volumes-especially GTV – because rectal filling has a greater influence on cervix and superior vagina position. An analysis performed by van de Bunt et al., using serial MRI, showed a significant correlation between weekly changes in rectal filling and shifts of the GTV in AP direction ($P < 0.001$). No significant correlations have been observed in the other directions, although SI shifts were also described. Displacements of the CTV in AP and SI direction were found, but the correlations with the rectum was weak.[14]

Daily variations in rectal filling has been described by several authors. An average rectal volume at start of treatment of 58 ml (range, 35–88 ml) was reported by Collen et al. van de Bunt et al. reported an average rectum volume of 78 ml (25–143 ml), median volume 69 ml; while Jadon et al. collected ranges of 21–150 ml. However, all authors agree that there are no significant differences in rectal filling volume between the start and end of treatment, neither systematic changes.[10,14,18] In regards to the measurements within the anteroposterior diameter of the rectum, Eminowicz et al. showed interesting data. They reported an inverse relationship between rectal anterior-posterior diameter and bladder volume. The coverage of CTV1 (uterus and cervix) was unsatisfactory with AP diameter >4.5 cm vs. 3.6 cm. The possibility that the PTV covered the entire CTV was reduced by 5.8% with each mm of deviation of the rectum in the AP direction. At the same time, this probability is greater if the rectum is wider in the treatment than in the simulation.[23]

2.1.3. *Reduction in tumor volume and shape deformation*

Reduction in tumor volume as tumor response, is a determining effect because it drastically alters the position of organs and structures between each other. In their study of 16 patients with locally advanced cervical cancer, Chen et al. observed that the volume and location of the cervix changed significantly during the course of treatment, and concluded that tumor regression occurs mainly between the second and third week of treatment, needing an adaptive new treatment plan.[24] Table 1 depicts some of the cervix shrinkage values reported in literature.

There are also changes in organs shape, especially in uterus and in bladder capacity filling (elsewhere explained here). Bondar et al. analyzed a series of patients in an attempt to predict the variation in shape of the uterus, concluding that it is possible to predict the position and shape of the uterus if the volume in the bladder is known/controlled. As described above, the uterus changes from anteverted to retroverted, as well as remarkable rotations are possible during treatment.[17,24,25]

2.2. *Planning target volume considerations*

Once ITV is known, an additional margin is required. The planning target volume (PTV) should include additional uncertainties. Dosimetric uncertainties and setup errors must to be considered in addition to organ motion and shape variations considered in ITV.[26]

Dosimetric uncertainties (penetration of beam, beam geometry, calculation algorithm) are a complex aspects in radiotherapy which can affect the treatment delivery and reproducibility; however, its analysis is beyond the scope of this review. Its knowledge, adjustments and possible

Table 1 – Sample of papers describing cervix shrinkage.

Author	Measuring tolls	Measurement time	Reduction value
Beadle et al.[22]	TC scan (weekly)	45 Gy	97 ml to 31.9 ml, mean volume reduction 62.3%.
Lee et al.[8]	Clinically, bimanual examination	30.8 Gy	50% reduction
Chen et al.[24]	CBCT (weekly)	48.6 Gy	79.62 ml to 20.86 ml

problems are the matter of physicist team at IMRT/IGRT protocol developing.

Setup errors are defined as the differences between the planned position and the position during delivery. They occur due to variations in fixation systems and/or patient's tatoo alignment, mechanical mismatches (laser miss aligning, couch rotation, etc.), staff expertise and time available to do the positioning.[26] A useful description of this kind of errors in pelvic radiotherapy is made by Kim et al., when analyzing 52 patients treated with IMRT or 3D conformal radiotherapy. Using 2D kV images and/or CBCT, they compared planned vs. on-treatment images finding a systematic and random errors of 1.1 mm, 2.3 mm, 2.3 mm and 3.9 mm, 5.0 mm, 3.5 mm in AP, ML and SI directions, respectively, suggesting a setup margin for CTV to PTV of 5.5, 9.1 and 8.3 mm in AP, ML and SI directions, respectively.[27] Besides 3D vector variation, rotational shifts have been identified. A retrospective analysis was made in 25 cervical cancer patients treated with IMRT radiotherapy for cervical cancer into EMBRACE protocol; at the end of the treatment, Laursen et al. analyzed the residual rotation error through a comparison using the CBCTs made during the treatment. A mean and standard deviation for the residual rotational errors obtained through retrospective offline registration were $0.04^\circ \pm 1.40^\circ$, $-06^\circ \pm 0.9^\circ$, and $0.04^\circ \pm 0.9^\circ$ for pitch, yaw and roll, respectively, resulting in a target shift larger than 5 mm in 57 of the 650 treatments evaluated.[28] A demonstration of how this setup errors can affect the clinics was reported by Xin in 170 cervical cancer patients; all these patients underwent pelvic IMRT, but in a group of 86 patients a strict CBCT protocol was conducted and shifts corrected online, getting a significant reduction of comparative toxicity.[29]

3. IGRT solutions

Many studies relevant to IGRT have been published which offer different solutions to reduce the risk of geographical failure, as well as decrease the inclusion of unnecessary healthy tissue. Consequently, IGRT is, above all current methods, the best strategy to reduce setup uncertainties, if accompanied by adequate patient preparation, reproducible positioning, appropriate margins, the use of verifying images during treatment and fiducial placement.

3.1. *Preparation*

There is scarce literature about recommendations related to the preparation of patients for virtual simulation and treatment. Eminowicz et al. conducted a retrospective study in which they suggest bladder and rectal filling volumes and timing for verifying images. An ideal planning volume for the bladder will be between 150–300 ml, achieved by the authors with 3 cups of water and 30 min of waiting time, but they considered shortening it to 20 min in the days of concomitance. Additionally, they suggest an adequate hydration throughout the entire treatment. Regarding rectal preparation, they found the administration of laxants for planning and during the entire treatment to be useful, depending on Bristol stool scale (type 1–3 twice daily laxant, 4–5 once a day, 6–7 no laxant). If a rectal diameter is more than 4 cm, micro enemas should be used. However, these measures are not enough without the regular verifying images.[23] Previously, Chan's protocol had proposed to evacuate urine 1 hour before each scan and treatment, followed by the intake of 500 ml of water to achieve a reproducible bladder filling. For rectal reproducibility they also recommend administration of magnesium hydroxide the night before, unless GI toxicity exist.[9]

3.2. *Positioning*

The use of conventional techniques, prone position and Belly Board (BB) have been considered a strategy to reduce irradiation of the small intestine volume (SIV). Hence, some authors have compared this to the supine position using IMRT techniques, highlighting Adli et al. and Stromberger et al. studies. They reported a reduction in SIV receiving more than 45 Gy, from 19 to 12.5% and 20.3 to 13.7%, respectively, but with an increase of 9.9% of the large intestine and rectum irradiated.[30,31] In 2012, Wiesendanger-Wittmer et al. reported the impact of the position and the BB in a systematic review of the literature on pelvic tumors. This review shows that the prone position contributes to diminishing SIV irradiated when compared with the supine position, being even greater when BB is added. A theoretical impact could be expected on a reduction of GI toxicity.[32] Additionally, other systems have been developed to displace the small intestine, based on compression with Styrofoam, and are also used in conjunction with the prone position and the BB, reducing the SIV between the PTV from 67.9 to 16.8% (P 0.00002). No changes in the rectum or bladder were seen, when the IMRT technique was added.[33,34]

3.3. *Margins*

In a review by Jadon et al., internal margins were proposed in order to assure movements of the cervix.[10] Data from nine studies with 176 patients were summarized. In some of these publications isotropic margins between 15.3 and 21 mm around the CTV are suggested, but most of them proposed anisotropic margins from 12 to 32 mm on the AP axis, 8 to 20 mm SI and 7 to 17.5 mm ML (Table 2). All of these publications used different imaging modalities at different moments.[9,14,16–18,20,33,35,36]

Van de Bunt et al. showed statistically significant differences between patients' rectum filling above and below 70 ml, recommending different margins for each group.[14] Wang et al.

Table 2 – Proposed margins summary.

	Anterior (mm)	Posterior (mm)	Superior (mm)	Inferior (mm)	Left	Right	Craneocaudal	Anteroposterior	Lateral	Around cervix	Around uterus
Collen 2010	0.4 ± 10.1[f]	3 ± 6.9[f]	2.2 ± 8[f]	0.5 ± 5[f]	3.5 ± 4.9[f]	0.2 ± 4.5	0.2 ± 2.3[e]	1.1 ± 1.3[e]	−0.3 ± 1.6[e]		
Patnj 2017							10.3	5.8	5.6		
Maemoto 2017					3.3 ± 2.9	3.0 ± 2.3	7.6 ± 5.9	8.3 ± 6.3			
Wang 2012										4[a] 19[b]	5[a] 32[b]
Chan 2008										0.45[a] 15[b]	10[a] 40[b]
Schippers 2014	7[c]	8[c]	7[c]	9[c]					7 medial and 4 lateral[c]		
Van de Bunt 2008	12[f] 24[d]	14[f] 17[d]	4[f] 11[d]	8[f] 8[d]	11[f] 16[d]	12[f] 12[d]					
Tyagi 2011										15 around CTV	
Taylor 2008							15[d]	15[d]	7[d]	7[c]	
Lim 2009										5 from PTV with daily IGRT	
Williamson 2016										15 CTV1 10 CTV2 5–7 CTV 3	
Velema 2012										>10[c]	
Kim 2011										7[c]	
Khan 2012	20[d]	10[d]	10[d]	10[d]	10[d]	10[d]				13[d]	

[a] Isotropic margin intrafraccion.
[b] Isotropic margin interfraction.
[c] Around ganglia.
[f] From GTV.
[e] From uterus.
[d] From CTV.
CTV1: GTV + cervix + uterus.
CTV2: parametria + upper half vagina.
CTV3: pelvic nodes.

proposed a 5 mm margin at the body and 4 mm at the cervix, in order to include 95% of the CTV during intrafraction movement while wider margins of 32 mm (body) and 19 mm (cervix) are required for interfraction changes. This way, PTV must expand respectively to include these uncertainties.[16] Chan et al. suggested broader margins of up to 4 cm in the uterine fundus and 1.5 cm in the exocervix to ensure interfraction movements and 1 cm and 0.45 cm intra-fraction, respectively, with daily soft-tissue imaging to correct for interfractional motion or adaptive replanning.[9] Taylor et al. proposed an asymmetrical margin with CTV–PTV expansion of the uterus, cervix and upper vagina of 15 mm AP, 15 mm SI and 7 mm laterally and expansion of the nodal regions and parametria by 7 mm in all directions.[17]

Moreover, Tyagi et al. showed how a 15 mm isotropic margin failed to encompass the entire CTV in 32% of the fractions. However, the mean volume 'missed' was 4 ml.[35] A further virtual study modeled three scenarios, with results favoring a tapered CTV-to-PTV margin that increases around the fundus. This would restore fundus and CTV dose to desired levels, but would increase normal tissue volumes receiving doses in the range 30–50 Gy by a further ~5%. In sum, when uterine motion is large and compensated for with a tapered margin, normal tissue volumes receiving doses in the range 30–50 Gy increase by up to 13%.[37]

Conversely, Lim et al. suggested a 5 mm margin allowed for pelvic organ motion with adequate dose delivered to 98% of the CTV in 95% of patients. But, one patient had significant underdosing due to unpredictable target motion.[13] Moreover, Williamson et al. tried to validate models to justify strategies to define PTVs. Their results showed that 95% isodose line completely encompassed 92.3% of all CTVs (95% CI 88.3–96.4), not significantly different from the 95% probability anticipated a priori ($P = 0.19$). The total proportion of missed CTV was small, mostly the mean of covered CTV was 99.9%, and 95.2% misses were located in the anterior body of the uterus. So, definitely, with the clinical implementation of a previously proposed PTV definition strategy based on a shape model for intact cervical cancer, the probability of CTV coverage was high and the volume of CTV missed was low. This PTV expansion strategy is acceptable for clinical trials and practice; however, they recommend daily image guidance to avoid systematic large misses in select patients.[38]

Regarding nodal internal margins, evidence is scarce. Velema et al. mentioned that with the current clinical margin, adequate coverage of the nodal CTV cannot be guaranteed for all patients. These findings emphasize the need to determine accurate CTV-to-PTV margins for the nodal CTV in highly conformal IMRT of cervical cancer patients.[39] In their paper, Schippers et al. reported pelvic and retroperitoneal nodes motion. Seventeen patients with visible nodes on MR images underwent T2-weighted MR scans before and weekly during the course of IMRT. Nodal volume regression from the pre-treatment condition to week 4 was 58% on average (range: 11.7% increase to 100% decrease). Nodal volumes partly increased between the pre-treatment scans and the scans in weeks 1–3, but in week 4 all nodes except one had regressed. Around the nodal volumes manually derived ITV margins accounting for volume changes and position shifts of 7.0, 4.0, 7.0, 8.0, 7.0 and 9.0 mm to the medial, lateral, anterior, posterior, superior and inferior directions were needed to cover 95% of all nodes. These margins should be taken into consideration when planning external beam radiotherapy (EBRT) boosts, especially for highly conformal boosting techniques. With these contradictory information, a 1 cm margin is deemed as sufficient in one study and insufficient in another.[21] Consensus guidelines, still, suggest a 7 mm CTV to PTV margin for nodal volumes.[7]

Another strategy was proposed by Khan et al. to optimize PTV margin. Using data from CT planning and CBCTs, they modeled the CTV variations; 758 landmarks were placed over the planning CTV and vectors from these superimposed on CBCTs, so PTV definition according to surface marking led to improving CTV coverage with narrow PTV margins.[40]

3.4. CBCT

CBCT images and MVCT are the most commonly used IGRT systems in clinics. Collen et al. took MVCT to measure changes in the cervix, such as an average and standard deviation by anterior $0.4\,mm \pm 10.1\,mm$, posterior $-3\,mm \pm 6.9\,mm$, superior $2.2\,mm \pm 8\,mm$, inferior $0.5\,mm \pm 5.0\,mm$, left $3.5\,mm \pm 4.9\,mm$ and right $0.2\,mm \pm 4.5\,mm$. Variations at the uterine level were greater as discussed above. From their experience, they suggest daily use of MVCT, as an alternative that allows to make adjustments in the positioning.[18]

Another recommendation is to perform at least CBCT once a week for organ motion monitoring plus daily verification of bladder filling with a bladder scan or CBCT if bladder scan is not available.[23]

In addition, a study carried out with 105 patients with gynecological malignancies assessed CBCT once a week for IMRT and daily for IGRT/VMAT. A total of 2078 CBCT images were studied. The margins of PTV volume were calculated from the variations in the setup. The setup variation was 5.8, 10.3, and 5.6 mm in AP, SI, and ML direction. This allowed adequate dose delivery to the CTV and the sparing of organs at risk. The researchers concluded that daily kV-CBCT is a suitable method of accurate patient positioning with high-precision techniques, preventing geographic miss.[26]

3.4.1. *Fiducial markers*

Implanted fiducial markers (FM) can facilitate fast detection of interfraction and intrafraction tumor motion in the treatment of cervical cancer. Previous experiences with implanted markers in the cervix were characterized by the loss of markers and the presence of significant scatter artifacts in CT scans; marker loss rates of 14–42% were found using a fluoroscopic electronic portal imaging device (EPID) and radiopaque markers to detect internal cervix movement.[41] FM (tantalum, gold and polymeric) were used in five studies. Good marker visualization was reported with planar kilovoltage imaging (90% visualized) and CBCT (100%).[10] Mens et al. placed 4 to 6 polymeric markers in the fornices of the vagina. It turned out to be a very reliable method with hardly any marker loss during RT and with a marker localization between 90% and 100% in the kV images and CBCT, respectively. Even after cervix-uterus is shrunk, a constant distance was maintained between the individual markers and the surface of the cervix uterus. These led them to suggest that this is a reliable method to

track inter and intrafraction motion during treatment.[42] Moreover, cervix interfraction motion was measured in fifty cervical cancer patients assessed by daily CBCT imaging with a new polymeric marker. They evaluated visibility, artifacts and FM loss. First, sufficient visibility of the markers was verified. Streaking artifacts for the new markers were reduced compared to conventional gold markers. Marker loss was minimal during treatment: in only 3 of the 50 patients, one marker was lost. Second, systematic and random displacement of the marker was recorded and analyzed in three dimensions with regard to the planning CT and the first CBCT, showing similar displacement with respect to other published data and good reproducibility.[11]

3.4.2. *Adaptation*

Adaptive radiotherapy plans seem to be essential in targets with large variability because of rapid tumor response, changes in size and/or organ motion. Cervix cancer is a good example of it.

Lee et al. described how carcinoma of the cervix involutes rapidly with chemoradiotherapy and high dose rate (HDR) brachytherapy. The time for 50% tumor regression was calculated to be 21 days and occurs after 30.8 Gy.[8]

In 2011 and 2012 Bondar's papers individualized model-based ITV accounting for the cervix and uterus motion. Bladder volume changes were generated by using a motion-model constructed from two pretreatment CT scans (full and empty bladder). For the majority of patients, the anticipated error was below the margin encompassing the cervix-uterus motion; the population-based approach was 38 mm and 7 to 10 mm for the individualized strategies. This strategy could be used to create a patient-specific ITV and to support online adaptive strategies.[25,43]

Based on their previous findings, the concept of plan of the day was introduced by the same group. Thus, the creation of a plan library per patient is based on the choice of an appropriate plan for every treatment session based on the imaging of each day. In other words, plan libraries were generated using scans with variable bladder filling (and hence different uterine positions) and the plan of the day chosen was based on bladder volume. Adaptive approach was reproducible and increased OAR sparing, compared with non-adaptive methods.[44]

More recently, Chen et al. found significant variations in tumor regression and spatial location occurred during treatment. GTV decreased during the course of radiation therapy ($P < .001$) from 79.62 ml at prior treatment to 20.86 ml at the end of external radiotherapy. CTV changed to some degree from 672.59 ml to 608.26 ml, and the uterine volume (UV) changed slightly from 83.72 ml to 80.23 ml. The mean percent volume changes ranged from 23.05% to 70.85% for GTV, 4.71% to 6.78% for UV, and 5.84% to 9.59% for CTV. Changes in GTV-correlated with the RT ($P < .001$). Actually, adaptive radiotherapy approaches are necessary to improve treatment accuracy for cervical cancer.[24]

These data indicate that adaptation is a possible solution and an important strategy to ensure accuracy with less-toxicity treatment.

3.4.3. *Other potential solutions*

As far as we know, no study has directly compared offline versus online imaging strategies for the management of organ motion. Taking into account the large interfraction variability reported in the literature, an offline review does not seem to be appropriated to correct at the right moment possible setup shifts.

In addition, uterine sleeve placement allowed to document the median and maximum ranges of cervical mobility during the treatment course of RT to be 8–16 mm and 23–36 mm, and at the time of HDR brachytherapy to be 5–12 mm and 11–32 mm, respectively.[8,45] Furthermore, Jan et al. data about sleeve application during the course of thomotherapy and brachytherapy could be used as a surrogate marker for localization of the tumor before daily IGRT.[46]

Lou et al. documented comparisons of bladder scanner (BS) with CT, CBCT, and an ultrasound diagnostic device (iU22). A consistent and reproducible bladder volume (BV) is acquired by using a portable BS. Hence, the target displacement and CTV-to-PTV margin can be both reduced in the supero inferior direction but had little or no effect in the anterior–posterior and right–left directions. With BS the BV deviated by 1.4% in accuracy. There were no difference between the measurements of the BS and the iU22. The BV measured by the BS was strongly correlated with actual urine volume, as well by CT or CBCT, $P < 0.05$. The BV increased by 3.7 ± 1.0 ml/min, which depended on the amount of water ingested by the patient ($R = 0.96$, $P < 0.05$). The authors were able to reduce the workload related to the measurements by using individual patient information including the patient's age, water-drinking amount, time at which water-drinking began, and patient's diet.[47]

4. Discussion

This non-systematic review summarizes relevant data published from three level of evidence which highlights the challenges facing cervical IMRT treatment, such as cervical/uterine motion, reduction of GTV as tumor response and the impact of bladder and rectal filling. The purpose is to offer a general vision of the main steps to be taken into account by each clinical facility wanting to introduce this technology.

Selection of appropriate contours and margins is mandatory. In the majority of the studies reviewed, margins were presented only in terms of PTVs, although, all of them explained and measured internal organ motion as well as setup uncertainties. We rather present margins in terms of ITV and PTV separately, as a way to emphasize the importance of position displacements, changes in alignment, beam geometry and all the other setup uncertainties different from organ motion. Even though these aspects were not treated in depth; identifying, measuring and correcting them, should be a priority when establishing IGRT local protocols. However, designing an ITV is optional if PTV includes "all" uncertainties.[48] Definitely, the margins are affected more by the movement of the uterus than by the movement of the cervix, because the uterus is more prompt to rotational and translational changes in greater proportions. Some data indicates a maximal AP uterine motion of 48 mm and 32 mm in SI direction.[17] Interfraction

motion is more pronounced than intrafraction motion, but both most be taken into account within ITV margins. Therefore, based on this information, a larger uterine margin and a smaller cervical margin, would probably include the different movements described.

Bladder filling has more impact on uterine motion and rectal filling more impact on cervical and vaginal motion. During treatment, bladder undergoes changes in daily volumes and filling capacity. Thus, patients with bulky locally advanced tumors could have difficulties in bladder filling (Fig. 1, DICOM files). We have not found reports about how these aspects affect the bladder itself, in terms of radiation exposition and risk of toxicity. A full bladder could have an advantage in decreasing its mean dose and V45–50, but it is not reproducible. An empty bladder is more reproducible, but would imply the opposite, in terms of dose exposition. According to this, a comfortably full bladder could have clinical and dosimetric benefits to protect the organ itself, as well as sparing doses at intestine and rectum.

Gynecological radiotherapy treatments are carried out in a prone or supine position. There is no rule, but a prone position is normally recommended in postoperative scenario while supine is used in primary treatments. The advantages of one over the other seem to be greater for 3D conformal radiotherapy than for IMRT.[32] In the literature reviewed and commented in this paper, there are no firm recommendations of one or the other. In fact, the measures and analysis presented by the authors deal with patient positioning, both in prone and supine (some did not even mention it). We identified a relatively greater number of patients positioning in supine but it is not possible to make any analysis or recommendation based on this. We consider supine position superior in terms of reproducibility, patient's comfort and is easier for the staff to evaluate organ motion or filling. The dosimetric advantages of prone position in terms of intestine dose sparing are at the expense of greater dose in rectum; although the intestine is more sensitive to radiation damage, the rectum is closer to the targets and is exposed throughout the treatment (even at brachytherapy). We reserved prone position in primary treatment of cervical cancer, just when intestine doses are not controlled by bladder filling and IMRT/IGRT solutions at supine position.

Even though FM had demonstrated adequate reliability in clinical practice, they only identify the upper vagina and cervix position but not represent the motion of the other pelvic organs and targets (parametrial tissue, uterus, ganglia, bladder, etc.).[41] Because of the complexity described in pelvic IMRT, we do not recommend FM alone as a IGRT solution. CBCT permits a more complete evaluation of all pelvic organs, thanks to its ability to show soft tissue in addition to bone and/or FM. Patient positioning, setup displacement, bladder and rectal filling and target motion can be evaluated easily with this IGRT solution. Perhaps, CBCT has a limitation in time of execution, staff training and intrafractional tracking, that can be improved by combining it with FM. CBCT alone, or in combination with FM are the most widespread and complete IGRT solutions to put into daily practice.

Defining the adequate margins to CTV-ITV-PTV is probably the most difficult and relevant task in the preparation of IGRT protocol. Thus, we found it hard to summarize all existing information on this topic. We found a lot of heterogeneities between the different consulted papers: time to do the measures, techniques used, methodology to measure and/or to analyze data; patient's race, patient's age, clinical tumor stage, position at the couch and technology available, among others. We can just suggest 2 things after our own analysis: 1. Anisotropic margins: in trying to choose not to narrow, not to large margins, it is a fact that each CTV and organs inside the pelvis have a different range of motion to take into account in ITV; 2. Select and review by your own the literature which best suits your population and facility aspects at the time of choosing your margins. Our review is not a systematic one, which poses a certain limitation. We performed a detailed search in databases and included the only one systematic review found that suits our parameters. Nevertheless, some useful studies may have been omitted here. Supported by all data presented, but based on our interpretation, and on our own experience and practice, we offer our recommendations in Table 3.[50]

We think that modifications in contouring guidelines could be required to facilitate the implementations of anisotropic/asymmetrical margins in clinics. Perhaps, defining a high risk CTV (HR-CTV) for IMRT/IGRT treatments including GTV and the entire cervix, as in brachytherapy contouring guidelines, could be practical. It would allow separating the uterus (the most mobile target) from CTV1 and creating a different volume to it, therefore, different ITV margins to cervix and uterus. In addition, an HR-CTV could be useful at the time of brachytherapy to analyze and compare plans, doses, tumor shrinkage and areas at risk, among others.

A consensus guidelines is expected, which will have to include recommendation about minimum equipment, quality assurances, contouring and safety margins. At the moment IGRT/IMRT is not the standard on practice, so randomized trials on adative IGRT/3D versus IGRT/IMRT are also required.

Table 3 – Authors recommendation.

	Recommendation
Position	*Supine*. Better reproducibility, patient comfort.
Bladder filling	*Comfortably full bladder*. Drink 500 ml of water and wait 30 min
Rectum preparation	*Empty rectum*. Transverse diameter <4 cm. Oral laxative and/or microenemas according to Bristol stool chart []
TC planning	TC with empty and comfortably full bladder.
Contouring	Contour ITV to CTV1 using both TC planning.
Adaptive	*Re-planning at 3th treatment week*. Significant tumor and ganglia shrinkage.
Technique	*Volumetric IMRT (VMAT)*. Faster delivery = less intrafraction motion.
IGRT solution	*Daily CBCT*. Optional: add FM.

Conflict of interest

None declared.

Financial disclosure

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rpor.2018.05.002.

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