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Adjuvant volumetric-modulated arc therapy with simultaneous integrated boost in endometrial cancer. Planning and toxicity comparison

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Abstract

Objective. To report dosimetric and acute toxicity data in prospectively enrolled high-intermediate risk endometrial cancer (HIR-EC) patients postoperatively irradiated by simultaneous integrated boost volumetric modulated arc therapy (SIB-VMAT). *Methods.* Thirty prospectively enrolled HIR-EC patients were postoperatively treated by SIB-VMAT. Target coverage, dose homogeneity, and sparing of organs at risk (OARs) were compared with corresponding data retrieved from an historical control (30 consecutive selected matched patients) treated by concomitant boost three-dimensional conformal radiotherapy (3D CRT CB) from a previously published study (ADA-I trial). All patients received 45 Gy on pelvic lymph nodes plus 10 Gy boost on the vaginal vault. *Results.* The SIB-VMAT technique produced more inhomogeneous plans than 3D CRT CB, but showed significantly better conformity index (CIs) for both PTVs. SIB-VMAT was associated with significant reduction in the irradiated small bowel (SB) volume compared with 3D CRT CB for all dose range >10 Gy (e.g. V_{15}: 163.5 cm^3 vs. 341.3 cm^3, $p = 0.001$ and V_{40}: 43.8 cm^3 vs. 85.2 cm^3, $p = 0.008$). With regard to bladder and rectum, SIB-VMAT showed a significant sparing advantage at all dose levels with respect to 3D CRT CB retrieved plans. Moreover, overall OARs D_{mean} were significantly reduced by the SIB-VMAT ($p = 0.001$). According to CTCAE v.4.0, acute (within three months) GI toxicities were more frequent in 3D CRT CB versus SIB-VMAT (90.0% vs. 66.7%; p-value 0.028). *Conclusions.* Compared to data from a historical database of patients administered 3D CRT CB, SIB-VMAT significantly improves the dose conformity and sparing of OARs in HIR-EC patients undergoing postoperative radiotherapy. The improvement in terms of acute toxicity justifies further prospective clinical evaluation.

Postoperative radiotherapy tailored to high-risk prognostic factors may be indicated in endometrial cancer (EC) patients according to pathologically assessed findings [1,2]. Notwithstanding the irradiation technique improvements, gastrointestinal (GI) toxicity is still judged the Achilles' heel of radiotherapy. In fact, in EC postoperative radiotherapy the small bowel (SB) and rectal volumes lie in the target concavity (the so-called horseshoe shape), and cannot be adequately reduced by a three-dimensional conformal radiotherapy (3D CRT CB). Therefore, the exposition of true pelvis contents to the prescribed dose, together with the close anatomical relationship between the boosting site (vaginal vault) and the rectum are considered an intriguing challenge for radiation oncologists in the planning setting.

Intensity-modulated radiation therapy (IMRT) could represent a valid option since it allows the dose

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to be highly conformed to the target while constraining the dose to healthy tissue. IMRT techniques also allow the simultaneous delivery of different doses to different target volumes within a single fraction, the so-called simultaneous integrated boost (SIB) technique. This strategy has been used to increase dose per fraction to the boost volume, keeping the elective volume dose at a lower level, and providing clinical and dosimetric advantages [3]. Several studies on gynecological cancers have demonstrated the safety and the efficacy of IMRT in terms of toxicity in different clinical settings [4,5]. Moreover, emerging data on oncologic outcomes and morbidity profile demonstrated the advantages of postoperative IMRT in the management of high-risk EC patients [6,7]. Yet, there is still reluctance to adopt IMRT as standard practice in EC, due to increased treatment time and cost.

More recently, volumetric-modulated arc therapy (VMAT), a novel form of IMRT, has been developed: in this "fully dynamic" technique, the gantry is rotating while the beam is on, and dose rate, shape of the beam, and speed of rotation continuously change [8]. Various planning studies in several anatomic sites showed that VMAT has the potential to generate plans with similar quality to conventional IMRT but with a large reduction in treatment time and in the number of monitor units (i.e. the measure of machine output) [9–11].

Concerning treatment of high-intermediate risk endometrial carcinoma (HIR-EC) patients, a concomitant boost 3D CRT CB technique has been adopted in our department on the basis of our previous results from ADA-I trial, which showed toxicity and clinical outcome figures similar to those reported for standard ERT plus BRT [12,13]. In the context of our continuing efforts to decrease the GI toxicity rate in EC, by means of irradiation technique modifications [14–16], we launched a new phase I–II clinical trial in our center which has replaced the 3D CRT CB with SIB-VMAT. This study (ADA II trial), aimed at addressing the rate of late GI toxicity, is currently ongoing and is expected to complete the enrolment within December 2014.

In this paper, we present the preliminary analysis of dosimetric and acute toxicity in patients who were treated with 45 Gy on pelvic lymph nodes and 55 Gy on the upper two thirds of vaginal vault by SIB-VMAT. To provide a direct comparison with patients treated with the same radiotherapy doses otherwise administered by 3D CRT CB, the corresponding clinical data from ADA-I trial patients, were retrieved [12]. In particular, in order to reduce the selection bias eventually related to the time frame of enrolment, the last 30 consecutive patients treated in the ADA-I trial and the first 30 consecutive patients treated in the ADA-II protocol were selected for comparison in terms of planning results and acute toxicity.

Patients and methods

Eligibility

According to new FIGO staging and high-intermediate risk classification as presented in Portec trial [2] histological proven endometrioid EC patients with: 1) age greater than 60 years and stage 1B grade 1–3 disease, or stage 1A grade 3 disease; and 2) stage 2A-IIIC2 disease, any age were included. Pretreatment work-up was previously described [12]. All patients underwent hysterectomy and bilateral adnexectomy ± pelvic lymphadenectomy. Adjuvant treatment was prescribed following NCCN guidelines v.2.2010 [1] for treatment of uterine cancer. Patients signed an informed consent for inclusion in this study, approved by the local Ethics Committee. Exclusion criteria were: presence or uncontrolled pelvic inflammation. Adjuvant chemotherapy before radiotherapy was allowed, if indicated. No concomitant chemotherapy was planned.

Radiotherapy

Four to six weeks after surgery or chemotherapy completion, patients underwent to pelvic elective nodal irradiation plus boost to the vaginal vault over 25 fractions along five weeks. Set-up, contouring, plan evaluation, toxicities assessment and follow-up were the same for patients enrolled in ADA-I as well as in ADA-II trial. Treatment planning and dosimetric verification were different according to the two different irradiation techniques and we detailed below.

Set-up

Simulation and treatment were performed in prone position using an up-down table device (UDT), aimed at reducing SB volume in the treatment field. Moreover, full bladder and empty rectum during simulation and irradiation were required in order to keep SB out of the boost field and to increase treatment reproducibility. A computed tomography (CT) scan, with contrast filling of intestine, was used for radiotherapy planning in all patients.

Volume of interest definition

Pelvic volume [clinical target volume 2 (CTV2)] was defined as upper two thirds of the vagina (if not

involved) or the whole vagina (if involved at pathologic evaluation), obturator lymph nodes, external iliac nodes, internal iliac nodes, and presacral nodes. To account the organ motion and set-up uncertainties a planning target volume 2 (PTV2) was defined adding 8 mm margin to the CTV2. The boost volume (PTV1) consisted of the upper two thirds of vagina plus resection lines in the parametria (CTV1) as delineated on the planning CT scan with an 8 mm margin. Contouring was performed according to the Radiation Therapy Oncology Group (RTOG) consensus guidelines [17].

OARs were contoured as follows: 1) the SB was defined as all intestinal loops below the 5th lumbar vertebra; 2) the bladder was entirely contoured with no distinction between the wall and its content; and 3) the rectum was contoured from the rectosigmoid to the anorectal junction.

Treatment planning

All plans were generated with Masterplan Oncentra treatment planning system and delivered by an Elekta Precise Linear Accelerator (Elekta, Crawley, UK).

ADA-II plans (SIB-VMAT technique) were generated using the optimization process described in [10–18]. In this study, all VMAT plans were set up in the 'dual arc' modality. The prescribed doses were 55.0 Gy to PTV1 and 45.0 Gy to PTV2, which were delivered simultaneously over 25 daily fractions. This resulted in daily fractions of 2.2 Gy for PTV1 and 1.8 Gy for PTV2. Plans were optimized using PTVs and OARs dose objectives/constraints listed in Supplementary Table I (available online at http//www.informahealthcare.com/doi/abs/10.3109/0284186X.2013.819997). 98% of the PTVs volume have to receive a dose $>$ than 95% of prescription dose, i.e. >42.75 Gy for PTV2 and >52.25 Gy for PTV1 delivered in 25 fractions, respectively.

The ADA-I treatment planning process (3D CRT CB technique) was previously described [12]. Briefly, two plans, one for each PTV, were independently optimized. Dose calculations were separated in a dose prescription of 45 Gy for PTV1 and PTV2, and a dose prescription of 10 Gy for PTV1 alone, to be both administered in 25 fractions. This resulted in daily fractions of 2.2 Gy for PTV1 and 1.8 Gy for PTV2.

Dose specifications and nomenclature were according to the ICRU report 62. For all patients, set-up reproducibility was daily checked as previously described [19]. For quality assurance through treatment planning and delivery, two independent checks were performed by medical and physics staff, as previously reported [20].

Plan evaluation and comparison

All plans were compared using dose-volume histograms. The mean dose (D_{mean}), the target volume receiving more than 95% of prescribed doses ($V_{95\%}$), the near-minimum ($D_{98\%}$) and near-maximum ($D_{2\%}$) doses were scored for PTVs. The dose homogeneity to the PTV was expressed by an homogeneity index (HI) defined as $HI = 100 \times (D_{2\%}-D_{98\%})/Dp$, where Dp is the prescribed dose. Two conformity indexes, CI_1 and CI_2, defined as the volume encompassed by the 95% isodose divided by the PTV volume, were calculated for PTVs. Lower CI and HI values indicated a better conformity and homogeneity of the dose to targets.

SB avoidance was evaluated by the mean dose, $D_{2\%}$ (i.e. the dose administered to 2% of the organ volume) and the absolute organ volume receiving doses at various levels; rectum and bladder avoidance were evaluated by the D_{mean} and the absolute organ volume receiving doses at various levels.

Dosimetric verification

SIB-VMAT underwent to more accurate physical checks than 3D CRT CB plans. The delivered doses were measured using the Seven29 ion chamber array [21] and the Octavius phantom [22]. SIB-VMAT plans were recalculated on phantoms representing the Octavius geometry and density and the doses were measured both on coronal and sagittal planes for every arc. A comparison of measured versus calculated dose distributions was carried out with PTW Verisoft software v4.0, using the gamma index evaluation. Pretreatment dosimetry was considered optimal if the percentage of points fulfilling gamma index criteria ($P_{\gamma 1}$) exceeded 95% using 3% for dose criterion and 3 mm for the distance to agreement criterion. Average and maximum values of the gamma index were also considered for comparison.

Toxicity assessment

Radiation-related toxicity was assessed prospectively. Acute adverse events were defined as those adverse events occurring from day 1, or commencement of radiation therapy, through day 90. All effects seen after 90 days from the beginning of radiation therapy were considered late effects. In our paper we refer to acute adverse events. Grading of toxicity was based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, with the highest grade of any observed toxicity reported for each patient during treatment or within the first three months following treatment. A radiation oncologist evaluated patients once a week during the RT and one month

after treatment. The follow-up schedule was detailed reported in [12].

Statistical analysis

The t-test for independent samples and χ^2-test were used to compare dosimetric and acute toxicity data between the two treatment techniques with statistical significance assumed for $p < 0.05$. Statistical analyses were carried out using Systat v.10.2 (Systat for Windows, Software Inc. 2002).

Results

Patient characteristics

Clinico-pathological characteristics of the two groups are reported in Table I. Patients did not differ for age, body mass index (BMI), performance status (ECOG), FIGO stage and grading. About 60% of patients underwent extrafascial hysterectomy, while 40% received radical hysterectomy. Route of hysterectomy was mostly laparotomic (68.3%), but in a minority of patients was laparoscopic (26.7%), or vaginal (5%). Systematic pelvic lymphadenectomy was performed in 58.3% of patients, while 41.7% underwent lymph node sampling (10%) or no lymphadenectomy at all (31.7%). Twenty-four patients (40%) received adjuvant chemotherapy before radiotherapy due to stage and/or unfavorable histology.

Target coverage

Table II shows an overview of all the investigated parameters for the two target volumes. The plan objectives (98% of PTVs volume to be irradiated by more than 95% of the prescribed doses, i.e. $D_{98\%} > 95\%$) for PTVs coverage were achieved with both techniques. Moreover, also the PTV1 $D_{2\%}$ constraint aimed to reduce hot spots ($D_{2\%} < 107\%$) was respected. The SIB-VMAT technique produced more inhomogeneous plans for PTV1 than 3D CRT CB ($p < 0.001$), but showed significantly better CIs for both PTVs ($p < 0.001$). An example of isodose distributions is shown in Figure 1 that clearly shows the SB sparing by the SIB-VMAT plans.

Organs at risk constraints

The 3D CRT CB and SIB-VMAT mean volumes of SB, rectum, and bladder are reported in Table III. Concerning SB, 5 Gy-step volumes (from $V_{5\ Gy}$ to $V_{50\ Gy}$) were analyzed. SIB-VMAT was associated with significant reduction in the irradiated SB volume compared with 3D CRT CB for the majority of volume constraints analyzed (V_{10}: 384.7 cm^3 vs. 281.7 cm^3, $p = 0.021$; V_{15}: 341.3 cm^3 vs. 163.5 cm^3, $p = 0.001$; V_{20}: 313.2 cm^3 vs. 125.7 cm^3, $p = 0.001$; V_{25}: 269.9 cm^3 vs. 100.3 cm^3, $p = 0.001$; V_{30}: 161.2 cm^3 vs. 79.7 cm^3, $p = 0.002$; V_{35}: 107.6 cm^3 vs. 62.1 cm^3, $p = 0.013$; V_{40}: 85.2 cm^3 vs. 43.8 cm^3, $p = 0.008$; V_{45}: 48.4 cm^3 vs. 13.5 cm^3, $p = 0.006$). In

Table I. Patient characteristics.

	SIB-VMAT	3D CRT CB	
	N° (%)	N° (%)	p-value[a]
Patients	30 (100)	30 (100)	n.s.
Age,yrs (median; range)	63; 45–84	62; 42–77	n.s.[b]
BMI (mean ± standard deviation)	29.9 ± 6.1	30.5 ± 4.5	n.s.[b]
ECOG			
0	26 (86.6)	28 (93.3)	n.s.
1	4 (13.4)	2 (6.7)	
FIGO stage and grading			
IA G3	4 (13.3)	5 (16.7)	n.s.
IB G1-3	11 (36.7)	6 (20.0)	
II any G	8 (26.7)	7 (23.3)	
III any G	7 (23.3)	12 (40.0)	
Route of hysterectomy			
Laparotomic	16 (53.3)	25 (83.3)	0.025
Laparoscopic/vaginal	14 (46.7)	5 (16.7)	
Lymphadenectomy			
Systematic pelvic ± aortic	20 (66.6)	15 (50.0)	n.s.
None/lymph node sampling	10 (33.4)	15 (50.0)	
Adjuvant CT before RT			
yes	12 (40.0)	12 (40.0)	n.s.
no	18 (60.0)	18 (60.0)	

BMI, body mass index; CT, chemotherapy; n.s., not significant; RT, radiotherapy.
[a]calculated by Fisher's exact test for proportion; [b]calculated by Wilcoxon rank sum non-parametric test.

Table II. Dose statistics comparison for planning target volumes (PTVs) and treatment efficiency (mean ± standard deviation).

	SIB-VMAT	3D CRT CB	p-value
PTV1			
D_{mean} (Gy)	56.21 ± 0.60	55.87 ± 0.66	0.041
$D_{2\%}$ (Gy)	58.27 ± 0.88	56.71 ± 0.72	0.001
$D_{98\%}$ (Gy)	53.03 ± 0.76	54.73 ± 0.50	0.001
$V_{95\%}$ (%)	99.1 ± 0.9	99.9 ± 0.0	0.001
HI_1	9.1 ± 2.1	4.6 ± 1.0	0.000
CI_1	1.5 ± 0.2	2.8 ± 0.2	0.001
PTV2			
D_{mean} (Gy)	48.95 ± 0.75	49.10 ± 0.76	n.s.
$D_{98\%}$ (Gy)	43.51 ± 1.39	44.07 ± 0.67	*0.054*
$V_{95\%}$ (%)	98.3 ± 1.6	99.7 ± 0.9	0.001
CI_2	1.7 ± 0.2	2.9 ± 0.2	0.001
Treatment efficiency			
Monitor unit number	592 ± 68	195 ± 21	0.001
Delivery time (min)	4.9 ± 0.3	5.0 ± 0.2	n.s.

Figure 1 is graphically shown the SB volumes irradiated at representative isodoses for both techniques. In addition, the SB D_{mean} was significantly reduced with the SIB-VMAT (15.803 Gy vs. 12.132 Gy, $p = 0.036$).

Concerning bladder and rectum sparing, SIB-VMAT showed a significant advantage if compared with 3D CRT CB. SIB-VMAT technique was superior with respect to bladder (D_{mean}: 51.158 Gy vs. 44.464 Gy, $p = 0.001$; V_{40}: 95.2 cm^3 vs. 70.9 cm^3, $p = 0.001$; V_{50}: 72.6 cm^3 vs. 36.8 cm^3, $p = 0.001$; V_{55}: 19.1 cm^3 vs. 13.3 cm^3, $p = 0.038$), as well to rectum (D_{mean}: 50.755 Gy vs. 44.847 Gy, $p = 0.001$; V_{40}: 90.9 cm^3 vs. 71.5 cm^3, $p = 0.001$; V_{50}: 66.0 cm^3 vs. 34.1 cm^3, $p = 0.001$; V_{55}: 29.7 cm^3 vs. 9.2 cm^3, $p = 0.001$) for each analyzed dosimetric parameter.

Delivery efficiency and accuracy

The number of monitor units for SIB-VMAT was a factor of 3.0 higher than for 3D CRT CB (592 vs. 195, $p = 0.001$). The mean total treatment time was 4.9 minutes for double arc SIB-VMAT, compared with 5.0 minutes for 3D CRT CB. Pretreatment verification was carried out for all the 120 VMAT arcs (four per patient, each arc was irradiated twice, once in the coronal plane and then in the sagittal plane). With criteria equal to 3%-3 mm, the measurements of 120 arcs showed an agreement with calculated values with a mean gamma value of 0.39 and on average 95.9% of the measured points with gamma values lesser than 1.0.

Acute radiation toxicity

Acute skin, GI, and genitourinary (GU) toxicity were the most frequently reported (Table IV): we did not find any significant difference in the distribution of skin toxicity (any grade) between the two treatment groups; however, GI adverse events were more frequent in 3D CRT CB versus SIB-VMAT (90.0% vs.

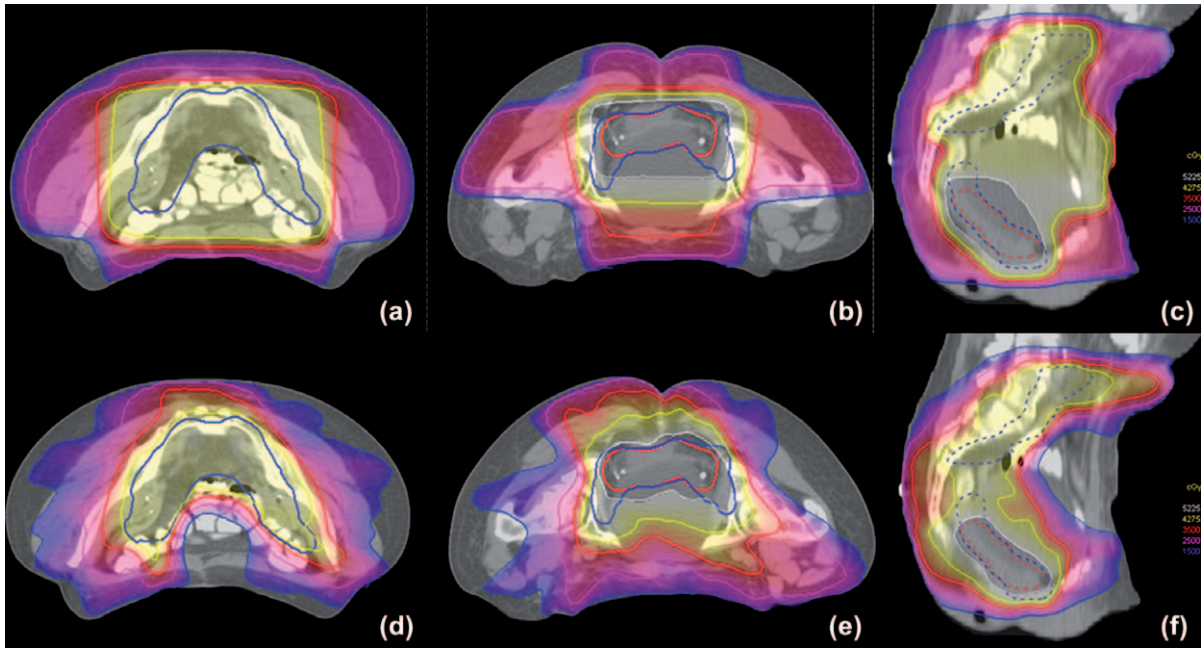

Figure 1. Axial, and sagittal view of 3D CRT CB (a, b, c) and SIB-VMAT (d, e, f) representative isodose distributions on PTV2 (blue contour) and PTV1 (red contour). Yellow ($V_{42.75}$) and white ($V_{52.25}$) isodoses correspond to 95% of PTVs prescription dose. Red (V_{35}), pink (V_{25}) and blue (V_{15}) isodoses correspond to low-intermediate dose levels. Sparing of the contrast-enhanced small bowel and bladder by the SIB-VMAT plans is clearly visible.

Table III. Dose statistics comparison for organs at risk (mean + standard deviation).

	SIB-VMAT	3D CRT CB	p-value
Small bowel			
Volume (cm^3)	736.0 ± 285.3	868.7 ± 357.5	n.s.
D_{mean} (Gy)	12.13 ± 5.26	15.80 ± 7.77	0.036
$D_{2\%}$ (Gy)	48.35 ± 4.88	48.16 ± 3.40	n.s.
$V_{5\ Gy}$ (cm^3)	435.6 ± 181.2	486.3 ± 238.4	n.s.
$V_{10\ Gy}$ (cm^3)	281.7 ± 130.1	384.7 ± 198.6	0.021
$V_{15\ Gy}$ (cm^3)	163.5 ± 85.5	341.3 ± 181.2	0.001
$V_{20\ Gy}$ (cm^3)	125.7 ± 67.7	313.2 ± 170.2	0.001
$V_{25\ Gy}$ (cm^3)	100.3 ± 55.3	269.9 ± 149.6	0.001
$V_{30\ Gy}$ (cm^3)	79.7 ± 47.7	161.2 ± 128.1	0.002
$V_{35\ Gy}$ (cm^3)	62.1 ± 40.8	107.6 ± 86.7	0.013
$V_{40\ Gy}$ (cm^3)	43.8 ± 31.5	85.2 ± 76.5	0.008
$V_{45\ Gy}$ (cm^3)	13.5 ± 13.7	48.4 ± 63.6	0.006
$V_{50\ Gy}$ (cm^3)	0.9 ± 4.1	6.3 ± 20.1	n.s.
Bladder			
Volume (cm^3)	268.7 ± 133.1	234.2 ± 144.6	n.s.
D_{mean} (Gy)	44.46 ± 4.57	51.16 ± 2.10	0.001
$V_{40\ Gy}$ (%)	70.9 ± 17.3	95.2 ± 7.1	0.001
$V_{50\ Gy}$ (%)	36.8 ± 19.7	72.6 ± 18.4	0.001
$V_{55\ Gy}$ (%)	13.3 ± 7.3	19.1 ± 13.0	0.038
Rectum			
Volume (cm^3)	75.2 ± 18.1	87.8 ± 43.5	n.s.
D_{mean} (Gy)	44.85 ± 3.74	50.75 ± 2.73	0.001
$V_{40\ Gy}$ (%)	71.5 ± 17.2	90.9 ± 10.0	0.001
$V_{50\ Gy}$ (%)	34.1 ± 15.4	66.0 ± 18.5	0.001
$V_{55\ Gy}$ (%)	9.2 ± 5.5	29.7 ± 15.2	0.001

66.7%, respectively; p-value 0.028). Also, the rate of Grade ≥ 2 GI toxicity appears higher in 3D CRT CB versus SIB-VMAT (30.0% vs. 16.7%, respectively; p-value 0.439), and consisted more frequently in tenesmus (n = 7 in 3D CRT CB vs. n = 4 in SIB-VMAT patients, p value 0.366). Other Grade 2 GI toxicities included six (10%) patients with diarrhea (n = 5 in 3D CRT CB, and n = 1 in SIB-VMAT, p-value 0.102), and two (3.3%) anal bleeding in 3D CRT CB. Although in SIB-VMAT patients the route of the hysterectomy has been preferentially laparoscopic, the type of surgery was not significantly associated to the acute GI Grade ≥ 2 toxicity rate (p-value 0.29, data not shown).

There was no difference in genitourinary toxicity (any grade) between the two treatments (56.7% of in 3D CRT CB vs. 63.3% in SIB-VMAT); Grade ≥ 2 GU toxicity (mainly dysuria, urgency, increased frequency) showed a trend to be more frequently represented in 3D CRT CB (n = 8, 26.7%) versus SIB-VMAT (n = 2, 6.7%) patients, although the statistical significance was not reached (p-value 0.058). As far as other toxicities are concerned, mucosal and hematological side effects were only rarely documented, and mostly consisted of Grade 1 toxicity; the rate of leukopenia was higher in 3D CRT CB versus SIB-VMAT (40.0% vs. 16.7%, respectively, p-value 0.045). However, it has to be taken into account that Grade > 2 leukopenia was documented only in patients treated with chemotherapy before radiation, and was not differently distributed between the two groups.

Discussion

To the best of our knowledge, this is the first paper reporting dosimetric as well as toxicity data on SIB-VMAT in HIR-EC patients; the comparison of current results with those coming from an historical control represented by HIR-EC patients postoperatively administered the standard 3D CRT CB approach (ADA-I trial) [12] allows the reader to better appreciate SIB-VMAT performance.

With respect to the PTVs coverage, statistical analysis confirmed a substantial overlap of the two techniques. The higher conformity together with the lower homogeneity (due to the presence of hot spots

Table IV. Acute toxicity of the two groups (CTCAE v.4.0 scale).

	Acute toxicity					
	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	Any grade n (%)	p-value*
Skin SIB-VMAT	17 (56.7)	5 (16.7)	0 (0)	0 (0)	22 (73.3)	
Skin 3D CRT CB	12 (40.0)	8 (26.7)	1 (3.3)	0 (0)	21 (70.0)	n.s.
Gastrointestinal SIB-VMAT	15 (50.0)	5 (16.7)	0 (0)	0 (0)	20 (66.7)	
Gastrointestinal 3D CRT CB	18 (60.0)	8 (26.7)	1 (3.3)	0 (0)	27 (90.0)	0.028
Genitourinary SIB-VMAT	17 (56.7)	2 (6.7)	0 (0)	0 (0)	19 (63.3)	
Genitourinary 3D CRT CB	9 (30.0)	8 (26.7)	0 (0)	0 (0)	17 (56.7)	n.s.
Mucosal SIB-VMAT	5 (16.7)	2 (6.7)	0 (0)	0 (0)	7 (23.3)	
Mucosal 3D CRT CB	3 (10.0)	1 (3.3)	0 (0)	0 (0)	4 (13.3)	n.s.
Leukopenia SIB-VMAT	1 (3.3)	3 (10.0)	1 (3.3)	0 (0)	5 (16.7)	
Leukopenia 3D CRT CB	8 (26.7)	3 (10.0)	1 (3.3)	0 (0)	12 (40.0)	0.045
Anemia SIB-VMAT	1 (3.3)	0 (0)	0 (0)	0 (0)	1 (3.3)	
Anemia 3D CRT CB	3 (10.0)	1 (3.3)	0 (0)	0 (0)	4 (13.3)	n.s.

Numbers in brackets are percentages calculated on 30 available cases for each group.
*calculated by Pearson χ^2-test, any grade toxicity versus none.

in the target volume) observed in SIB-VMAT plans compared to 3D CRT CB is an intrinsic feature of intensity-modulated techniques, which in expert hands are not likely to either impact on the target dose objective, or play any clinical relevance.

With regard to the OARs sparing, we showed that the SIB-VMAT was associated with a statistical significant reduction of mean doses across all healthy tissues examined, as also shown for IMRT in solid tumors including uterine neoplasms [3–7].

The most important results concerned SB sparing since the available literature relative to the tenual loops doses is relatively poor, especially when hypofractionation is used (2.2 Gy/day-SIB technique).

Emerging data suggested that the absolute volume of small bowel receiving >15 Gy should be held to <120 cm^3 when possible to minimize severe acute toxicity, if delineating the contours of bowel loops themselves. This threshold has been shown to predict a low risk of toxicity, in fact a strong direct correlation was found between the Grade 3 acute toxicity and the SB volume receiving >15 Gy, with rates of severe acute adverse events raising up to 30% and even to 70% when 150–299 cm^3 or >300 cm^3 of SB is irradiated to >15 Gy, respectively [23]. The clinical relevance of this effect relies in the potential harmful consequences of severe toxicity in terms of patient withdrawal from treatment, and decreased disease control. Concerning the $V_{15\ Gy}$ objective, we found that the irradiated SB was significantly reduced (almost halved) with SIB-VMAT compared to 3D CRT CB; moreover, the reduction of irradiated intestine by SIB-VMAT was constantly observed throughout the vast majority of dose/volume constraints when compared with 3D CRT CB, especially in the dose range of 10–45 Gy (Table III). This result has an important meaning particularly in low dose regions, and finds its clinical counterpart in the reduced GI toxicity by SIB-VMAT. Some concerns should be arisen about the significant difference in surgical procedures between the two groups (more invasive surgery in the 3D CRT group). Although, the route of the hysterectomy has been preferentially laparoscopic in SIB-VMAT patients, the type of surgery was not significantly associated to the acute Grade ≥ 2 toxicity rate (p-value 0.29).

Similar consideration can also be drawn for other OARs: indeed the bladder and rectal mean dose and dose/volume constraints were significantly lower with SIB-VMAT, thus confirming its dosimetric advantage. Long-term data will allow us to determine whether this would result in a lower incidence of late toxicity, particularly rectal one.

Few studies investigated on the use of arc radiotherapy in HIR-EC [11,24,25]. With the limits inherent in the small sample series, Wong et al. showed dosimetric and radiobiological benefits of intensity-modulated arc therapy (IMAT) in reducing SB irradiation [24]. Analogous findings were documented in the dosimetric study with two-axis conformal arc therapy [11] conducted on 10 EC patients. Despite dose uniformity and conformity being still inferior to those of IMRT, its simplicity and extensive availability combined with further improvement warrant it as a potential shortcut alternative to IMRT.

In a very recent prospective report on toxicity in gynecological (cervical = 25, endometrial = 41) cancer patients treated with postoperative radiotherapy using IMAT, Vandecasteele et al. [25] reported no Grade ≥ 3 GI and 2% Grade ≥ 3 GU toxicity in EC patients. Moreover, the authors observed Grade 2 GI and GU toxicities in 54% and 12% EC patients, respectively. The three most frequent symptoms for Grade 2 toxicity were frequency (49%), abdominal cramps (22%), and abdominal discomfort (12%) in EC patients [25]. Despite Vandecasteele's data on severe acute toxicity seem really comparable with ours, when Grade ≥ 2 toxicity is examined SIB-VMAT seems to ameliorate treatment results. In our series 16.7% and 6.7% of SIB-VMAT patients experienced GI and GU grade ≥ 2 toxicities, respectively. This finding may be related to a better OARs sparing obtained by the two arc technique as reported in Material and Methods section.

Furthermore, a major benefit in using VMAT compared to all other intensity modulated techniques lies in the delivery times significant reduction with its potential advantages in set-up errors control. This improvement is mainly related to the elimination of all the non-beam-on times, such as MLC movements required to realise the various segments of IMRT beams or gantry motion to reach the fixed position for 3D CT; in fact, with the VMAT technique it is possible to irradiate continuously while the gantry rotate around the patient. In our previous experience on rectal cancer [10], we compared VMAT technique with 3D CRT and fixed-field IMRT, in terms of target coverage and irradiation of organs at risk. The mean reduction in treatment time from 14 minutes (IMRT plans) to 5 minutes (SIB-VMAT plans) translates into a reduction in the whole treatment slot from 25 minutes to less than 15 minutes when patient set-up and positioning were considered. Also in the present study, the reduced treatment time increased patient compliance to treatment and potentially minimized the risk of intrafractional motion. In addition, the time gained was used to increase patient throughput or to ameliorate image guidance.

In conclusion, SIB-VMAT technique combines the advantages of IMRT (highly conformal dose distribution, OAR sparing, and SIB approach) and the advantages of 3D CRT CB in terms of fast delivery.

The results of this clinical dosimetric study showed that in the HIR-EC irradiation SIB-VMAT technique significantly improves the dose conformity and reduces overdoses allowing considerable sparing of critical organs such as small intestine, rectum and bladder. Acute toxicity was low and did not exceed Grade 3 for all examined OARs. With the limits inherent to the small number of patients, SIB-VMAT showed a protective effect when compared with 3D CRT CB technique in terms of acute toxicity. A careful, long term patient follow-up is in progress aimed at verifying whether the reduction in normal tissue irradiation would translate into a more favorable pattern of eventual late treatment-related toxicity.

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Supplementary material available online

Supplementary Table I.