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Original Article

Feasibility of hypofractionated pelvic radiotherapy with parametrial and nodal simultaneous integrated boost for locally advanced cervical cancers: dummy run for the HYACINCT trial

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ABSTRACT

Objectives: The HYACINCT trial will investigate the role of dose-adapted hypofractionated pelvic radiotherapy in patients with locally advanced cervical cancer who are ineligible for cisplatin. This dummy run evaluated the feasibility of the protocol treatment planning objectives using intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT).

Material and Methods: The HYACINCT protocol defines a set of guidelines for image acquisition, target and organ delineation, and treatment planning objectives. Fifteen dummy cases were prepared, five each for three levels of dose requirements: 40 Gy without boost, and with boost to 45 Gy and to 48 Gy. IMRT and VMAT plans were prepared for each case, evaluated and assigned penalty and compliance scores according to planning objectives, and subjected to quality control. IMRT and VMAT plans were compared in terms of treatment plan quality (target coverage, penalty, and compliance scores), and treatment delivery. Tumor extent (T-stage, T-score), nodal status, and PTV volumes (in cc) were examined as potential determinants of penalty and compliance scores.

Results: IMRT was able to meet the planning objectives for all but one case; and VMAT, for all cases. All plans passed the quality control check. IMRT and VMAT were equivalent in terms of target coverage and penalty and compliance scores, but the latter was associated with better treatment delivery. T-score was a determinant for the penalty score.

Conclusion: The HYACINCT radiotherapy protocol is feasible with either IMRT or VMAT. VMAT may be beneficial in more extensive cases, as measured by the T-score.

Trial Registration Number: NCT05210270

Keywords: Hypofractionation, Nodal boost, Cervical cancer

INTRODUCTION

Cervical cancer is the fourth most common malignancy among women.[1] While the standard of care for locally advanced cervical cancer (LACC) is radiotherapy with concurrent cisplatin (chemoradiation, CRT), followed by brachytherapy (BRT), the standard approach when cisplatin is contraindicated is not defined.[2]

Hypofractionation is a standard approach for intensifying radiotherapy for head-and-neck cancers when concurrent cisplatin could not be given. In LACC, there is only a phase 1–2 trial on hypofractionated (HF-) RT combined with concurrent fluorouracil and cisplatin[3] and two retrospective studies on HF-RT without concurrent chemotherapy.[4,5] All studies employed two-dimensional RT techniques.

Advances in RT techniques, such as intensity-modulation (including intensity-modulated radiotherapy, IMRT, and volumetric arc therapy, VMAT) and image-guidance, have resulted in better tumor coverage, organ-sparing, and toxicity profiles.[6–8] These can be used to safely administer additional doses, whether through sequential (SEB) or simultaneous integrated boost (SIB), to nodes that are expected to receive inadequate dose contributions from subsequent BRT.[9,10]

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The HYACINCT trial [NCT05210270][11] is a single-center phase 1/2 trial investigating the safety and effectiveness of HF-RT with or without nodal SIB in the management of LACC among patients who are ineligible for concurrent cisplatin. The protocol defines guidelines for image acquisition, delineation, and treatment planning objectives and prioritization. We performed a dummy run study (1) to determine the feasibility of the treatment planning objectives; (2) to determine dosimetric improvement with VMAT over IMRT technique in terms of target coverage, penalty and compliance scores, and treatment delivery; and (3) to identify determinants of penalty and compliance scores.

MATERIAL AND METHODS

The RT protocol for the HYACINCT trial has been previously described.[11] Elements that are pertinent to the dummy run are summarized in the following subsections.

Selection of dummy cases

Dummy cases were selected from our department database among the patients treated from January 2021 to February 2022, and the radiotherapy charts and CT datasets. Eligibility criteria were: cervical cancer stage IIIA-IIIC1, or IVA, per FIGO 2018 definitions, simulation CT slice thickness ≤ 3 mm, simulation CT scan range spanning at least L2 to 5 cm below the ischial tuberosities, moderately filled bladder (the dome up to 4 cm above the superior border of the symphysis pubis), and a rectal anteroposterior diameter ≤ 4 cm. Cases with para-aortic nodes were excluded.

Fifteen cases were purposively selected to represent different extents of tumoral and nodal involvement. Five cases each were selected for different dose level requirements: 40 Gy with no boost, 40 Gy with SIB to 45 Gy, and 40 Gy with SIB to 48 Gy. A dose of 45 Gy was prescribed to the parametria when necessary, and to internal and/or external iliac (lower pelvic) adenopathy, and 48 Gy to common iliac (upper pelvic) or inguinal adenopathy. These total doses were prescribed to be delivered over 15 fractions.

Target and organs-at-risk delineation

The target volumes were contoured on all CT slices on which the targets exist. The volume definitions were in congruence with the Gyn IMRT Consortium consensus guidelines,[12] 1993 ICRU Reports #50 and #62. A summary of the target volume and organs-at-risk (OAR) delineation and nomenclature is provided in Appendices 1 and 2.

The volumes (in cubic centimeter, cc) for the PTV_40, PTV_45, and PTV_48 were noted. When overlapping, the volumes of all higher dose PTVs were subtracted from all lower dose PTVs, to generate the volume (in cc) for the latter, and for purposes of dosimetry planning and evaluation.

Dose prescription

In all cases, 95% of the PTV should receive 95% of the prescribed dose, and the volume of hot spots (107%) should be minimized inside and outside the PTV. The prescribed dose is to be given in 15 fractions.

Treatment planning objectives

RT planning objectives are summarized in Table 1. The objectives were prioritized in this order: PTV, Spc_Bowel, Rectum, Bladder, Femur_Base, Sigmoid, and Marrow. Doses within 90% to 120% of the prescribed dose were accepted if prescribed OAR dose constraints were met.

Treatment planning

IMRT and VMAT plans were created by the same physicist for each case using the Eclipse® v. 16.1 (Varian Medical Systems) treatment planning system (TPS) for a Varian VitalBeam® linear accelerator, using 6-MV photons. Inverse planning was done via the TPS optimization window with Photon Optimizer (PO_16.1.0) as the algorithm and calculation model. Doses were calculated using Anisotropic Analytical Algorithm (AAA_16.1.0).

For the IMRT plan, a single isocenter was placed at the center of PTV_40. Seven coplanar beams evenly spaced at gantry angles of 220°, 265°, 320°, 45°, 90°, 140°, and 180°, were employed. Alternatively, the beams were placed at 230°, 265°, 320°, 40°, 95°, 130°, 180°. Sliding window multi-collimator leaf motion was used.

The treatment planning objectives were entered into the plan to facilitate dosimetric calculation and optimization. After an initial calculation, the dose objectives and priority values were adjusted in the optimization window to meet the treatment planning objectives. Gradient rings were employed to limit high-dose spillage outside the target volumes. Plan normalization values were adjusted as a final measure, as necessary.

For the VMAT plan, the isocenter was placed at the same location similar to that of the IMRT plan. Two full-rotation arcs (clockwise from 185° to 175°, and counterclockwise from 175° to 185°) were set up. Collimator angles used were 45° and/or 315°.

An initial VMAT plan was generated using the values attained for the planning objectives in the previously validated IMRT plan. This was further optimized using the same process for the inverse planning for the IMRT plans.

Table 1: Treatment planning objectives.

Name of structure	Dosimetric parameter	Per protocol	Acceptable variation	Unacceptable deviation
Target constraints				
PTV_40	D95% (Gy)	≥40.00	≥38.80	<38.80
	D97% (Gy)	≥38.80	≥36.00	<36.00
	D0.03 cc (Gy)	≤46.00	≤48.00	>48.00
PTV_45	D95% (Gy)	≥45.00	≥43.65	<43.65
	D97% (Gy)	≥43.65	≥40.50	<40.50
	D0.03 cc (Gy)	≤51.75	≤54.00	>54.00
PTV_48	D95% (Gy)	≥48.00	≥46.56	<46.56
	D97% (Gy)	≥46.56	≥43.20	<43.20
	D0.03 cc (Gy)	≤55.20	≤57.60	>57.60
Organ constraints (no boost)				
Bladder	D0.03 cc (Gy)	≤42.80	≤42.80	>42.80
	D50% (Gy)	≤38.50	<40.00	
	D75% (Gy)	≤34.50	≤35.56	
	D85% (Gy)	≤26.50	≤26.67	
Rectum	D0.03 cc (Gy)	≤42.80	≤42.80	>42.80
	D50% (Gy)	≤38.50	≤40.00	
	D75% (Gy)	≤34.50	≤35.56	
	D85% (Gy)	≤26.50	≤26.67	
Sigmoid	D0.03 cc	≤42.80	≤42.80	>42.80
Spc_Bowel	D0.03 cc (Gy)	≤42.80	≤42.80	>42.80
	V34.5Gy (cc)	≤100	≤250	>250
	V26.7Gy (cc)[a]	≤500	≤500	>500
Femur_Base	D0.03 cc (Gy)	≤42.80	≤42.80	>42.80
Marrow	Dmean (Gy)	≤34.00	≤34.00	>34
Organ constraints (with boost)				
Bladder	D0.03 cc (Gy)	≤49.00	≤49.00	>49.00
	D50% (Gy)	≤38.50	≤40.00	
	D75% (Gy)	≤34.50	≤35.56	
	D85% (Gy)	≤26.50	≤26.67	
Rectum	D0.03 cc (Gy)	≤49.00	≤49.00	>49.00
	D50% (Gy)	≤38.50	≤40.00	
	D75% (Gy)	≤34.50	≤35.56	
	D85% (Gy)	≤26.50	≤26.67	
Sigmoid	D0.03 cc	≤49.00	≤49.00	>49.00
Spc_Bowel	D0.03 cc (Gy)	≤49.00	≤49.00	>49.00
	V42.7Gy (cc)[a]	≤20	≤20	>20
	V34.5Gy (cc)	≤100	≤250	>250
	V26.7Gy (cc)a	≤500	≤500	>500
Femur_Base	D0.03 cc (Gy)	≤42.80	≤49.00	>49.00
Marrow	Dmean (Gy)	≤34.00	≤34.00	>34

[a]Optional

Treatment plan evaluation

Each treatment plan was evaluated according to target coverage, penalty scores, and compliance scores.

For the evaluation of target coverage, the conformity index (CI)[13] and the homogeneity index (HI)[14] were calculated:

Conformity Index:

$$CI = \frac{\text{Volume within 100\% isodose line}}{\text{Volume of PTV}}$$

Homogeneity Index:

$$HI = \frac{D_{2\%} - D_{98\%}}{D_{50\%}}$$

A larger CI value indicates better coverage of the prescribed dose, while a lower HI value indicates better dose uniformity.

A penalty point of 1 was given for each acceptable variation from the protocol-defined constraints, and 10, for each

unacceptable deviation. The penalty points were summated to generate the penalty score.

A compliance score of 5 was given when all constraints were achieved without deviations or variations; 4, with no deviations and ≤2 variations; 3, with no deviations and >2 variations; 2, with ≤2 deviations and any variation; and 1, with >2 deviations and any variation.

Optional constraints for Spc_Bowel that were defined only for benchmarking and monitoring purposes were not included in the penalty or compliance scores.

Determinants of penalty and compliance scores

The following variables were evaluated as possible determinants of penalty and compliance scores: tumor stage, nodal status (node-negative, node-positive with lower pelvic, upper pelvic, and/or inguinal nodes), T-score,[15], and PTV_40, PTV_45, and PTV_48 volumes (in cc). The T-score is a summation of the scores reflecting the involvement of 8 pelvic structures (cervix, left parametrium, right parametrium, vagina, bladder, ureter, rectum, and uterine corpus), in an ordinal scale of 0 to 3, corresponding to no involvement, to the greatest extent of involvement. These variables were evaluated against compliance and penalty scores using univariate and multivariate regression.

Treatment delivery evaluation

Each plan was evaluated according to its treatment efficiency and performance on quality assurance procedures.

The total monitor units (MUs) for each plan were recorded as a parameter for treatment efficiency.

All plans were subjected to patient-specific quality assurance procedures. Portal verification plans were created using the portal dosimetry module of the TPS. Portal dosimetry was used, and the acquired images were evaluated. Maximum and average dose differences of ≤1.0 calibrated units (CU) and ≤0.2 CU were considered acceptable. For the gamma analysis, a dose tolerance of 3% and distance to agreement (DTA) of 3 mm were acceptable. The percentage of gamma with values <1 should be ≥90%. Plans with fields that failed to meet the above criteria were redelivered with split fields and were subjected again to the above procedures. Total treatment times were recorded during the delivery.

Comparison of IMRT and VMAT

Using two-tailed paired t-test, the 7-field IMRT and dual-arc VMAT plans were compared in terms of treatment plan quality (target coverage in terms of CI and HI, penalty and compliance scores, and absolute values for each treatment planning objective), and treatment delivery (treatment efficiency in terms of total MUs), and performance during quality assurance procedures.

RESULTS

Dummy cases

The disease extent and target volumes for the 15 dummy cases are detailed in Table 2. FIGO stage distribution is as follows: IIIB, 5; IIIC1, 5; IVA, 5. Among FIGO Stage IIIC1, three were T2b, two were T3b; one had lower pelvic, one had upper pelvic, and three had upper and lower pelvic adenopathy. Among FIGO Stage IVA, two were node-negative, one had lower pelvic, and one had upper pelvic adenopathy. Median T-score was 9, ranging from 5 to 19.

For the 40-Gy cohort, median PTV_40 volume was 1753 cc (1180–2238). For the 45-Gy cohort, median PTV_40 volume was 1269 cc (894–1634); and median PTV_45 volume was 260 cc (243–338). For the 48-Gy cohort, median PTV_40 volume was 1568 cc (1279–2285); median PTV_45 was 8 cc (0–36); and median PTV_48 volume was 38 cc (20–40).

Treatment plan evaluation

For every case, all constraints were achieved without unacceptable deviations for either IMRT or VMAT, except for one – case 45-3, for which the best optimized IMRT plan had one deviation (pertaining to the PTV_40 D0.03 cc). In this case, VMAT was able to generate a plan without deviation.

For all the other cases, all constraints were achieved with one or multiple acceptable variations. For three cases, IMRT was able to generate a plan with only one variation (case 40-3, Rectum D50%; 40-5, Spc_Bowel V34.5 Gy; and 45-4, PTV_40 D0.03 cc). All VMAT plans had multiple acceptable variations.

Determinants of penalty and compliance scores

On univariate regression analysis, no significant determinant was identified for the compliance score for the IMRT and VMAT plans. Only the T-score was found to be a borderline statistically significant determinant for the penalty score for the IMRT plans (ß = 0.903, 95% confidence interval = −0.24 to 2.05, p = 0.079). No significant determinant was identified for the penalty score for the VMAT plans.

On multivariate analysis, T-score was found to be a significant determinant of the penalty score for the IMRT plans (ß = 1.11, 95% confidence interval = 0.15 to 2.07, p = 0.028).

Treatment delivery evaluation

All plans passed quality control, except for one IMRT plan – case 45-4, for which the area gamma was 89% in one gantry.

Table 2: Dummy cases: Disease extent and target volumes.

Case	FIGO Stage	T Stage	T-score								N status	Volume (cc)		
			Overall	Uterine cervix	Parametrium		Bladder	Ureter	Rectum	Uterine corpus	Vagina		PTV_40	PTV_45	PTV_48
					Left	Right									
40-Gy Cohort															
40-1	IVA	4a	12	3	1	1	1	1	0	2	3	N0	2238	0	0
40-2	IIIB	3b	7	3	1	1	0	0	0	1	1	N0	1753	0	0
40-3	IVA	4a	10	3	1	1	1	0	0	1	3	N0	1797	0	0
40-4	IIIB	3b	8	3	2	1	0	0	0	1	1	N0	1180	0	0
40-5	IIIB	3b	9	3	2	1	0	0	0	1	2	N0	1305	0	0
45-Gy Cohort															
45-1	IIIC1	3b	8	3	1	2	0	0	0	1	1	N1: LP	1269	243	0
45-2	IIIB	3b	8	3	2	1	0	0	0	1	1	N0	894	260	0
45-3	IVA	4a	19	3	3	3	3	2	0	2	3	N1: LP	1634	338	0
45-4	IIIB	3b	11	3	3	3	0	0	0	1	1	N0	1371	289	0
45-5	IVA	4a	13	3	2	3	0	0	2	1	2	N0	1197	251	0
48-Gy Cohort															
48-1	IIIC1	3b	12	3	2	2	0	0	1	1	2	N1: LP, UP	2285	26	30
48-2	IIIC1	2b	7	3	1	1	0	0	0	1	1	N1: LP, UP	1860	36	28
48-3	IVA	4a	12	3	1	1	1	1	0	2	2	N1: UP	1279	0	20
48-4	IIIC1	2b	5	2	0	1	0	0	0	1	1	N1: LP, UP	1376	8	40
48-5	IIIC1	2b	7	2	0	1	0	0	0	3	1	N1: UP	1568	0	23

FIGO, *International Federation of Gynecology and Obstetrics*; T, *primary tumor*; cc, *cubic centimeter*; N, *node*; PTV, *planning target volume*; N0, *node-negative*; N1, *node-positive*; LP, *lower pelvis*; UP, *upper pelvis*

The plan was rerun on split fields and subsequently passed the quality control.

For IMRT and VMAT plans, respectively, the area gamma values were 98.11% and 99.82% ($p = 0.003$); the average gamma values, 0.30 and 0.19 ($p < 0.001$); the maximum dose differences (calibration unit, CU), 0.22 and 0.40 ($p < 0.001$); and the average dose differences, 0.02 and 0.04 ($p < 0.001$).

Comparison of IMRT and VMAT

The comparisons between IMRT and VMAT are summarized in Tables 3a and 3b. The average CI and HI values were not statistically different for the IMRT and VMAT plans, except for the HI for the PTV_40, which was significantly lower for the IMRT plans (0.11 versus 0.13, $p = 0.009$).

The compliance and penalty scores were not statistically different for the IMRT and VMAT plans. Comparison of individual treatment planning objectives revealed statistically significant differences only in terms of the PTV_40 D95% (39.67 Gy versus 39.41 Gy, $p = 0.02$) and D97% (39.31 Gy versus 39.00 Gy, $p = 0.02$) values, and Femur_Base D0.03 cc (Right, 40.24 versus 38.79, $p < 0.005$; Left, 40.08 versus 39.13, $p < 0.07$).

VMAT plans were associated with better efficiency: lower average total MUs (2599.90 versus 839.81, $p < 0.001$) and treatment delivery times (8.93 versus 2.76 min, $p < 0.001$).

DISCUSSION

The HYACINCT trial will investigate the role of hypofractionated RT with nodal boost in improving treatment outcomes among patients with LACC who are not eligible to receive cisplatin.

Hypofractionation is theoretically associated with loss of therapeutic ratio due to the lower alpha-beta ratio for normal tissue (a/ß = 3), when compared to cervical carcinomas (a/ß = 10). However, this could be offset if hypofractionated RT is given using conformal RT, which affords more conformal doses to the target volume and adequate organ sparing. Further, intensity-modulated RT (IMRT) allows for more homogenous dosimetry and delivery of higher doses to select target volumes. Volumetric arc therapy (VMAT) is an intensity-modulated technique that delivers the treatment using arcs rather than via a number of fixed beam angles and could theoretically allow for even better conformity and homogeneity. Image-guided radiotherapy (IGRT) entails more advanced imaging, such as on-board CT, to verify patient setup. It allows for accounting for internal motion and therefore allows for tighter PTV margins.

IMRT, but not VMAT or IGRT, is now widely accessible in the Philippines, where the majority of cervical cancers remain

Table 3a: Treatment plan quality: IMRT versus VMAT.

		IMRT	VMAT	Paired t-test (two-tailed)
	N	Mean (SD)		P-value
Treatment plan quality				
Conformity Index				
PTV_40	15	1.03 (0.19)	1.02 (0.21)	0.74
PTV_45	8	0.94 (0.04)	0.91 (0.10)	0.45
PTV_48	5	0.71 (0.06)	0.64 (0.28)	0.70
Homogeneity Index				
PTV_40	15	0.11 (0.04)	0.13 (0.04)	**0.009**
PTV_45	8	0.06 (0.02)	0.08 (0.03)	0.07
PTV_48	5	0.07 (0.02)	0.09 (0.04)	0.36
Compliance score	15	3.33 (0.62)	3.20 (0.41)	0.33
Penalty score	15	4.80 (4.35)	4.87 (1.88)	0.94
PTV_40				
D95% (Gy)	15	39.67 (0.47)	39.41 (0.49)	**0.02**
D97% (Gy)	15	39.31 (0.63)	39.00 (0.65)	**0.02**
D0.03 cc (Gy)	15	46.56 (1.28)	46.50 (1.54)	0.81
PTV_45				
D95% (Gy)	8	44.94 (0.23)	44.82 (53)	0.50
D97% (Gy)	8	44.84 (0.28)	44.67 (0.57)	0.39
D0.03 cc (Gy)	8	47.48 (2.94)	49.67 (1.04)	0.06
PTV_48				
D95% (Gy)	5	46.76 (0.20)	46.84 (0.17)	0.40
D97% (Gy)	5	46.52 (0.25)	46.64 (0.21)	0.21
D0.03 cc (Gy)	5	50.54 (1.11)	51.64 (2.16)	0.22
Bladder				
D0.03 cc (Gy)	15	44.79 (2.34)	45.09 (2.68)	0.18
D50% (Gy)	15	38.17 (1.20)	38.26 (1.01)	0.69
D75% (Gy)	15	30.50 (2.11)	30.50 (2.24)	0.99
D85% (Gy)	15	25.21 (1.49)	24.93 (1.55)	0.61
Rectum				
D0.03 cc (Gy)	15	43.74 (2.70)	43.88 (2.73)	0.82
D50% (Gy)	15	38.73 (0.59)	38.47 (0.67)	0.14
D75% (Gy)	15	33.21 (0.93)	32.88 (1.46)	0.25
D85% (Gy)	15	24.70 (1.97)	25.16 (1.61)	0.41
Sigmoid				
D0.03 cc (Gy)	15	43.96 (1.79)	43.86 (2.06)	0.70
Spc_Bowel				
D0.03 cc (Gy)	15	44.43 (2.29)	44.97 (2.31)	0.10
V42.7Gy (%)	10	5.71 (8.14)	6.13 (6.36)	0.76
V34.5Gy (%)	15	146.04 (42.39)	153.27 (47.03)	0.19
V26.7Gy (%)	15	291.80 584.47)	300.4 (85.78)	0.37
Femur_Base				
Right, D0.03 cc (Gy)	15	40.24 (2.26)	38.79 (2.14)	**<0.005**
Left, D0.03 cc (Gy)	15	40.08 (2.09)	39.13 (1.80)	0.07
Marrow				
Dmean (Gy)	15	27.94 (1.28)	28.28 (1.57)	0.20

Table 3b: Treatment delivery: IMRT versus VMAT.

		IMRT	VMAT	Paired t-test (two-tailed)
	N	Mean (SD)		P-value
Treatment delivery				
Total MU	15	2599.90 (718.12)	839.81 (161.70)	**<0.001**
Treatment delivery time (min)	15	8.93 (1.72)	2.76 (0.48)	**<0.001**
Area gamma (%)	15	98.11 (1.76)	99.82 (0.27)	**0.003**
Average gamma	15	0.30 (0.62)	0.19 (0.02)	**<0.001**
Maximum dose difference (CU)	15	0.22 (0.03)	0.40 (0.08)	**<0.001**
Average dose difference (CU)	15	0.02 (0.004)	0.04 (0.006)	**<0.001**

CU, *calibration unit*; MU, *monitor unit*

diagnosed at advanced stages, and many, with tumor-related renal complications. In the HYACINCT protocol, IMRT is intended to be the primary modality, so that the study protocol and outcomes could be applicable to most RT centers. Wider margins (15 mm for the uterus, cervix, and adnexae; 10 mm for the parametria; 7 mm for the elective nodal regions; and 5 mm for individual adenopathy) were used to account for internal motion, resulting in bigger volumes.

We conducted a dummy run to evaluate the feasibility of the RT protocol defined for this trial and the determinants of non-compliance, in order to inform patient selection for the pilot phase, as well as to evaluate the benefit of VMAT for cases that would not be feasible with IMRT alone. For this dummy run, we purposively selected cases of different tumoral volumes and topography. To quantify tumor topography, we used the T-score system as defined by Lindegaard *et al.*[15]

IMRT was able to meet the compliance criteria for all cases except for one, for which the maximum D0.03 cc within the PTV_40 was not met. This hot spot was located within the uterus, and this plan would have been accepted for clinical use. VMAT was able to generate compliant plans for all cases.

The CI and HI for the two techniques indicated similar dose conformity to target but statistically better dose homogeneity with IMRT. The difference is minimal and clinically negligible. The compliance and penalty scores were also similar. In terms of individual planning objectives, PTV_40 coverage (as indicated by D95% and D97%) was statistically better with IMRT, and femoral doses were lower with VMAT. The planner has greater control with IMRT compared to VMAT planning, and the statistically significant but clinically negligible differences in the average HI, D95% and D97% values are probably TPS-driven.

On the other hand, VMAT plans had more than three times lower total MUs and treatment delivery times. This means shorter treatment times, less intrafraction errors, better patient comfort, and higher machine throughput.

Overall, our findings affirm that the hypofractionated radiotherapy with nodal SIB protocol defined for the HYACINCT trial is feasible using either 7-field IMRT or dual-arc VMAT. The two are dosimetrically equivalent, but VMAT is associated with better treatment delivery. In a similar cohort where the pelvis was prescribed 50 Gy with nodal boost to 60 Gy, dual-arc VMAT was found to have better organ sparing compared to 7-field IMRT.[16] However, in contrast to our study, conventional fractionation (CF) and tighter PTV margins (5 mm) were used.

Among cohorts where the pelvis was prescribed 45–50 Gy CF without nodal boost, and using 7–10 mm margins, two studies that compared 7-field IMRT against single- or dual-arc VMAT found similar organ sparing, and only better treatment efficiency with VMAT,[17,18] consistent with our findings. On the other hand, two studies, one comparing 5-field IMRT and single-arc VMAT,[19] and the other, 9-field IMRT and dual-arc VMAT[20] found better organ sparing, conformity, and treatment efficiency with VMAT.

In a cohort where the pelvis and the para-aortic areas were prescribed 50 Gy without nodal boost, and using 7-mm margins, dual-arc VMAT was found to have better organ sparing, conformity, homogeneity, and treatment efficiency, when compared to 9-field IMRT.[21]

Among post-operative cohorts, two studies that compared 7-field IMRT and dual-arc VMAT both found the techniques to be dosimetrically equivalent, and better treatment efficiency with VMAT. In one, the pelvis was prescribed 45 Gy and 7 mm PTV margins were used;[22] in the other, 56 Gy, 10 mm.[23] On the other hand, one that compared 5-field IMRT and dual-arc VMAT found better organ sparing and treatment efficiency with VMAT.[24] The pelvis was prescribed 50 Gy and 10 mm PTV margins were used.

Overall, these studies indicate that VMAT is associated with better treatment efficiency and, for certain cases or protocols, better organ sparing. In our study, we hoped to identify determinants for non-compliance or for possible need for

VMAT. However, this pilot cohort, as in most of the above studies, included only 15 cases, and only one event of non-compliance was noted. Nevertheless, regression analysis identified the T-score, which reflects extent of involvement of the pelvic structures, as a significant determinant of the penalty score.

CONCLUSION

In summary, the results of our dummy run indicate that the hypofractionated radiotherapy regimen with nodal simultaneous integrated boost defined for the HYACINCT protocol, is feasible, whether with IMRT or VMAT. VMAT may be beneficial in cases with extensive involvement of the pelvic structures, as reflected by the T-score.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

Data availability statement

Data generated or analyzed in this study could be made available upon request, subject to approval by the University of Santo Tomas Hospital – Research Ethics Committee and the study team.

Authors' contributions

WB initiated the study, conceptualized the study design, participated in data collection and analysis, and drafted the manuscript. SC and MB participated in study design, data collection and analysis, and review and revision of the manuscript. MD participated in data collection. KB participated in study design, and review and revision of the manuscript. TO participated in study design, data analysis, and review and revision of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study final protocol was approved by the University of Santo Tomas Hospital – Research Ethics Committee (REC-2021-08-104-CT).

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Appendix 1: Target volume delineation and nomenclature.

Standard name	Description	Specification
GTV_40	Gross target volume to receive 40 Gy	GTV_40 will include all gross cervical disease determined from clinical and radiologic evaluations.
CTV_40	Clinical target volume to receive 40 Gy	Three sub-volumes will be defined and summed under CTV_40: CTVp1, CTVp2 and CTVn. CTVp1 will consist of the gross tumor, uterus, cervix, and adnexae; CTVp2, of the parametria and upper third of the vagina (or upper half, if the vagina is involved). If node-positive, the CTVn will extend up to aortic bifurcation, and 3 cm cranial to the gross nodal disease, and will include the ilio-obturator and presacral lymph nodes. It will include the mesorectal nodes if the rectum or mesorectum is involved. If node-negative, the CTVn will not extend above the aortic bifurcation, and will not extend lower than the superior limit of L5, and will include the ilio-obturator and presacral lymph nodes. The CTVn will be obtained by encompassing ~7 mm margin around the vessels, including any adjacent visible nodes, lymphoceles, or relevant surgical clips. The presacral nodes will be contoured until the superior border of the S3. The external iliac nodes will be contoured to the superior aspect of the femoral heads. The CTVn will exclude bone, muscle, and bowel and will not extend below the ischial tuberosities.
CTV_45	Clinical target volume to receive 45 Gy	The CTV_45 will include gross internal/external iliac nodes that will receive BT contribution, and the parametria, if parametrial boost is to be given.
CTV_48	Clinical target volume to receive 48 Gy	The CTV_48 will include gross common iliac, or inguinal nodes that will NOT receive BT contribution.
PTV_40	Planning target volume to receive 40 Gy	Three sub-volumes will be defined and summed under PTV_40: PTVp1, PTVp2, and PTVn. To generate the corresponding PTVp1, PTVp2, and PTVn, 15 mm, 10 mm, and 7 mm uniform expansions will be applied to CTVp1, CTVp2, and CTVn.
PTV_40-3 mm	Planning target volume to receive 40 Gy minus 3 mm from the skin (as needed)	The PTV_40 will exclude the 3 mm from the skin surface, if necessary, to spare the skin, while still encompassing the CTV_40 entirely within.
PTV_45	Planning target volume to receive 45 Gy	The PTV_45 will be generated by applying a 5 mm uniform expansion around CTV_45.
PTV_45-3 mm	Planning target volume to receive 45 Gy minus 3 mm from the skin (as needed)	The PTV_45 will exclude the 3 mm from the skin surface, if necessary, to spare the skin, while still encompassing the CTV_45 entirely within.
PTV_48	Planning target volume to receive 48 Gy	The PTV_48 will be generated by applying a 5 mm uniform expansion around CTV_48.
PTV_48-3 mm	Planning target volume to receive 48 Gy minus 3 mm from the skin (as needed)	The PTV_48 will exclude the 3 mm from the skin surface, if necessary, to spare the skin, while still encompassing the CTV_48 entirely within.

Appendix 2: Organ-at-risk delineation and nomenclature.

Standard name	Description	Specification
Spc_Bowel	All potential space that bowels may occupy.	Spc_Bowel will be contoured beginning from the axial slice 10 mm superior to the upper limit of the PTV and will continue to its most inferior extent in the pelvis. This will include the outermost extent of the bowel loops plus all potential space within the abdominal cavity that the bowels may occupy. Sigmoid and rectum will be contoured separately from the bowel.
Sigmoid	Sigmoid	The sigmoid will be contoured encompassing the entire structure to its outer walls, from the point where it leaves the left colic gutter up to the sigmoid flexure where it becomes the rectum, lodged in the mesorectum.
Rectum	Rectum	The rectum will be contoured encompassing the entire structure to its outer walls, from the point where it lodges into the mesorectum to the anus.
Bladder	Bladder	The bladder will be contoured encompassing the entire structure to its outer walls.
Marrow	Pelvic bone marrow	The marrow will be contoured to encompass the bone marrow in the iliac bones from the iliac crest down to the superior limit of the acetabulum, and will exclude the bone cortex.
Femur_Base_L Femur_Base_R	Femurs	The Femur_Base will be contoured to its outer bone contours, including only the femoral head and not including the femoral neck.