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Evaluation of the volumetric modulated arc therapy (VMAT) as alternative to the intracavitary brachytherapy boost treatment in locally advanced cervical cancer: retrospective study

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Original Article

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Abstract

Purpose: Intracavitary brachytherapy (IBT) is the standard boost treatment for patients with locally advanced cervical cancer. Volumetric modulated arc therapy (VMAT) boost serves as an alternative to IBT boost, but it has inferior target tumour coverage and organ at risk (OAR) sparing. In this study, a pear-shaped dose distribution was generated in the applicator-guided (AG)-VMAT boost on the existing IBT boost patient by an intercomparison with the existing VMAT boost practice.

Method: The treatment plan of eight patients treated with the VMAT boost and ten patients treated with the IBT boost was analysed. Then, the IBT boost CT images were exported from the OnCentra Brachytherapy treatment planning system (TPS) to Eclipse TPS to plan AG-VMAT boost to reproduce the pear-shaped dose distribution.

Result: AG-VMAT boost successfully reproduced the pear-shaped outline using the 100% isodose line from the IBT boost. The IBT boost treatment planning had the best dosimetry coverage for tumours by D_{90} 23·33 Gy and CI 1·00. The D_{2cc} of the bladder, rectum and femoral heads in the VMAT boost were in significantly higher doses than IBT and AG-VMAT boosts ($p \leq 0{\cdot}05$). The cumulative EQD_2 for the D_{90} in the IBT boost only fell within the tolerance limit. Meanwhile, the D_{2cc} of all the OAR doses in these three techniques was within the dose constraint set by the American Brachytherapy Society (ABS).

Conclusion: 24 Gy/3 fractions AG-VMAT boost successfully reproduced the pear-shaped dose distribution for D_{90} of the target, with D_{2cc} of the OAR remaining within the ABS limit.

Introduction

Cervical cancer is a global public health problem and the fourth most common cancer among women worldwide.[1] About 604,000 women were diagnosed with cervical cancer in 2020 and approximately 342,000 of them succumbed to the disease.[1]

The standard regimen for locally advanced cervical cancer includes concomitant external beam radiotherapy (EBRT) and weekly cisplatin chemotherapy, followed by a brachytherapy boost and intracavitary brachytherapy (IBT).[2] EBRT usually delivers 45–50 Gy to treat the tumour bed, parametria, and regional lymph nodes, while IBT escalates the dose to 80 Gy to 95 Gy to provide a boost to the gross tumour to prevent recurrences.[3] The inclusion of IBT in the treatment of locally advanced cervical cancer has shown a superior overall survival compared to EBRT alone.[4,5]

The IBT boost is an invasive technique that requires an applicator insertion into the body cavity. Its superiority is characterised by dose inhomogeneity, high tumour target coverage and the sharp dose gradient, which maximises the sparing of the organ at risk (OAR).[6] In IBT boost, an inhomogeneity pear-shaped distribution is created, leading to a higher central dose of upto 300% of the prescribed dose, while sparing the nearby tissues.[7] However, IBT boost has a few drawbacks. Firstly, it is highly dependent on the physician's skill. For example, improper applicator placement has been reported to reduce both local control (LC) and disease-free survival rates.[8] Secondly, IBT boost is very labour intense as it requires applicator insertion with general anaesthesia and extensive quality assurance measures.[7] Thirdly, IBT boost might associated with side effects such as pain and uterine perforation.[9]Moreover, patient refusal and unflavoured patient conditions such as large tumours, older age and anatomical configuration,

have contributed to the issues.[6] As a result, the IBT boost has gradually been replaced by EBRT boost techniques using intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) and stereotactic body radiotherapy (SBRT) techniques in the past decades.[3]

In our institution, the VMAT technique has been used as an alternative to the IBT boost to treat locally advanced cervical cancer because it can achieve highly conformal dose distribution while sparing the normal surrounding tissues.[10] Nevertheless, VMAT boost has inferior target coverage and OAR sparing, and it does not have the substantial dose inhomogeneity seen with IBT boost.[3] The homogenous dose distribution in VMAT boost has delivered 95–107% of the prescription dose to the planning target volume (PTV) without a high central dose.[11] Moreover, the radiation in the VMAT boost does not directly target the tumour as in IBT but must pass through the skin to reach the tumour. Furthermore, there is a splash of low dose to surrounding normal tissue in VMAT boost due to the utilisation of a higher monitor unit, which potentially increases the risk of secondary malignancies.[12] VMAT boost also changes the target volume position due to the internal target movement, resulting in the normal tissues being irradiated.[13] Hence, an applicator-guided VMAT (AG-VMAT) boost, with an applicator inserted in the vagina and uterus, is introduced to localise the gynaecological organs and other surrounding organs.[14]

Previous publications have undoubtedly rendered IBT the ultimate form of boost for locally advanced cervical cancer due to its superior target coverage and OAR sparing.[15–17] Hence, the current major issue in VMAT boost is to achieve a tumour dose coverage that is comparable to the IBT plans while sustaining OAR sparing. In this study, a pear-shaped dose distribution was proposed to be generated in the AG-VMAT boost technique on the existing IBT boost patient.

Materials and Methods

Patient selection

This study was a retrospective review of eighteen locally advanced cervical cancer patients who were referred to our institute between the years 2020 and 2023. All the patients received whole pelvis EBRT with a prescription dose of 45 Gy/25 fractions or 48·6 Gy/27 fractions, followed by 3–5 cycles of cisplatin or carboplatin. Ten patients underwent IBT boost using a Fletcher (consists of tandem and ovoid) applicator with the prescription dose of 21 Gy/3 fractions, 22·5 Gy/3 fractions or 18 Gy/2 fractions due to the different dose protocols practised in our institute over time. Meanwhile, eight patients received a 20 Gy/10 fractions of VMAT boost. The patient characteristics are shown in Table 1. Before conducting this study, approval was sought from the Human Research Ethics Committee of our institution.

Evaluation of IBT boost treatment plan

Firstly, 10 patients were inserted with Fletcher (consists of tandem and ovoid) applicator in the operation theatre with general anaesthesia. Then, a series of IBT boost computed tomography (CT) images were acquired using the Phillips Brilliance CT Big Bore 32 Slices (version 3·6 oncology) (Phillips Medical System, Cleveland, OH, USA) with a 2·5 mm slice thickness. The images were then transferred to the Oncentra treatment planning system (TPS) (V4·3·0·410) (Nucletron BV, Veenendaal, The Netherlands). The OARs, including the bladder, rectum, sigmoid, and left and right femoral heads, were delineated by the medical physicist. Following this, an IBT boost treatment plan was generated using a 5 mm step size and the Manchester system, where the dose was prescribed to point A. Point A is defined as 2 cm lateral to the tandem and 2 cm superior to the mucosa of the lateral fornix of the vagina, along the plane of the tandem.[18] The planned dose was then analysed. The 100% isodose line is defined as the 'high risk (HR)-clinical target volume (CTV)', which represented the tumour target for the IBT boost as shown in Figure 1.

Table 1. Patient and disease characteristics

Description	Number of patients (n)	Percentage (%)
Age (median: 51·5 years)		
≤ 50 years	9	50
> 50 years	9	50
FIGO Stage		
IIB	10	55·6
IIIA	1	5·6
IIIB	1	5·6
IIIC	4	22·2
IVA	2	11·1
Tumour Histology		
Squamous Cell Carcinoma	14	77·8
Adenocarcinoma	4	22·2

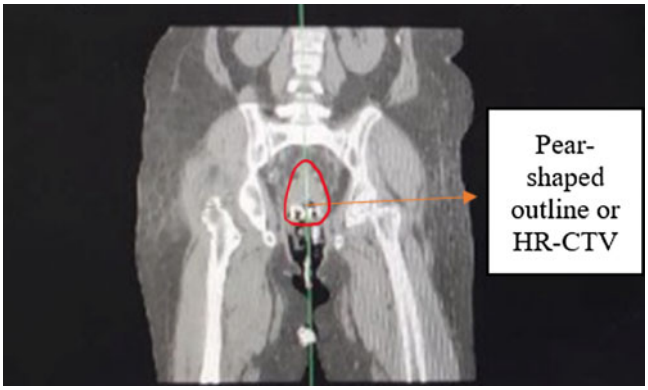

Figure 1. Pear-shaped outline was produced using the 100% isodose line in the existing intracavitary brachytherapy boost treatment plan.

AG-VMAT boost planning in eclipse TPS

For these patients, two plans were generated: IBT boost and AG-VMAT boost plans. The IBT boost CT image with the contouring was exported to the Aria Workstation for AG-VMAT boost treatment planning using Eclipse TPS V.13·6 (Varian Medical System, Inc. Palo Alto, CA, USA). In Eclipse TPS, the mass density of the Fetcher applicator was overwritten to density of water (1·00 g/cm^3) to exclude the attenuation of the applicator. The AG-VMAT boost treatment plan was created using one full arc (179°–181°) in a counterclockwise direction, with 6 MV photon energy, and a prescribed dose of 20 Gy/10 fractions. The HR-CTV

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Table 2. Dose constraint to organ at risk (OAR) for applicator-guided volumetric modulated arc therapy boost planning

OAR	Tolerance limit (Gy)
Bladder	D_{max} ≤23
Rectum	D_{max} ≤23
Sigmoid	D_{max} ≤23
Femoral heads	D_{max} ≤14

Table 3. Dose constraint to organ at risk (OAR) for hypofractionation schemes of applicator-guided volumetric modulated arc therapyboost based on Bisello et al.[19]

OAR	Tolerance limit (Gy)
Bladder	D_{max} <28·2 Gy
Rectum	D_{max} <28·2 Gy
Sigmoid	D_{20cc} <24 Gy
Femoral heads	D_{10cc} <21·9 Gy

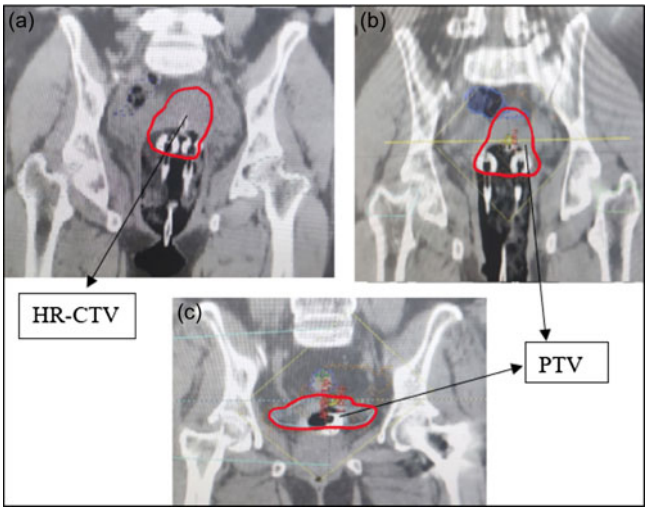

Figure 2. Pear-shaped target tumour in (a) intracavitary brachytherapy boost, (b) applicator-guided volumetric modulated arc therapy (AG-VMAT) boost, as well as an irregular planning target volume in (c) VMAT boost.

generated in Oncentra TPS was designated as PTV and the collimator angle was set at 45°. After setting all the parameters, optimisation was done for each plan.

For all the treatment plans, the PTV coverage had to exceed 95% of the prescribed dose (D95 ≥ 95%), and the hotspots were limited to 110% or less. Since no standard protocol exists for OAR dosing in AG-VMAT, our institution protocol was referred to in Table 2.

AG-VMAT boost planning analysis using hypofractionation

In the planned AG-VMAT boost for ten patients, different hypofractionation dose prescriptions, which were 20 Gy/5 fraction, 25 Gy/5 fraction, 20 Gy/4 fraction, 19·5 Gy/3 fraction, 24 Gy/3 fraction, 25·5Gy/3 fraction, were applied. The dose constraint for each treatment plan is shown in Table 3.

Evaluation of VMAT boost treatment plan

On the other hand, CT simulations were performed for eight patients (without the applicator in situ). The CT images were exported to the Aria Workstation using Eclipse TPS V.13 for VMAT boost treatment planning. The treatment plan was created using one full arc (179°–181°) in a counterclockwise direction, with 6 MV photons and a prescribed dose of 20 Gy/10 fractions. The planned dose was then analysed.

Dosimetric analysis in IBT, AG-VMAT, and VMAT boosts

IBT, AG-VMAT and VMAT boosts were evaluated using dosimetric parameters for the tumour target and OAR. For the tumour target, the dose to 90% of the target volume (D_{90}), conformity index (CI) and homogeneity index (HI) were used for comparison. For OAR, minimum doses of the most exposed 2 cm^3 volume (D_{2cc}) among the three boost techniques were compared. The formula of CI and HI is as follows:

$$CI = \frac{V_{95\%}}{volume\ of\ PTV} \quad (1)$$

where V_{95} is the target volume that encompasses a 95% isodose line.

$$HI = \frac{D_2 - D_{98}}{D_{50}} \quad (2)$$

where D_x is the dose received by x% of the target volume.

Then, Statistical Package for Social Science software version 26 was used to carry out the Kruskal-Wallis statistical test to analyse the dose differences for the target and OAR across the three boost techniques. The analysis indicated a significant difference when the p-value ≤ 0·05. Moreover, the accumulated dose from the EBRT and each boost technique was evaluated in terms of equivalent dose in 2 Gy per fraction (EQD_2) using $\alpha/\beta = 3$ Gy for OAR and $\alpha/\beta = 10$ Gy for tumour target. The dose-volume constraints for the accumulated dose to the tumour target were $D_{90} = 80$–90 Gy EQD_2, $D_{2cc} \leq 90$ Gy EQD_2 for the bladder, and $D_{2cc} \leq 75$ Gy EQD_2 for rectum and sigmoid as recommended by the American Brachytherapy Society (ABS). The formula for EQD_2 is as follows:

$$EQD_2 = D.\ \frac{d + \alpha/\beta}{2 + \alpha/\beta} \quad (3)$$

where D is the total dose (Gy) and d is the dose per fraction (Gy).

Result

Target delineation in IBT, AG-VMAT, and VMAT boosts

Figure 2(a) and (b) show pear-shaped HR-CTV and PTV in the IBT and AG-VMAT boosts, respectively. They had the same size and volume as they were appointed from the 100% isodose line in the IBT. However, in the real clinical setting, the shape of the PTV in the VMAT boost was irregular, conforming to the shape of the cervix (Figure 2(c)) rather than a pear-shaped distribution.

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Table 4. Comparison of dose to target and OAR between IBT, AG-VMAT, and VMAT boosts using the Kruskal–Wallis statistical test

Organ	Parameter	IBT boost (Mean ± SD)	AG-VMAT boost (Mean ± SD)	VMAT boost (Mean ± SD)	Kruskal-Wallis statistical test		
					p-value[a]	*p*-value[b]	*p*-value[c]
Tumour Target	D_{90} (Gy)	23·22 ± 2·00	20·34 ± 0·11	20·35 ± 0·14	0·023	0·034	0·897
	CI	1·00 ± 0·01	1·04 ± 0·03	1·02 ± 0·03	0·004	0·068	0·460
	HI	0·64 ± 0·01	0·08 ± 0·01	0·10 ± 0·03	<0·001	<0·001	0·009
Bladder	D_{2cc} (Gy)	15·21 ± 6·00	15·28 ± 3·08	20·38 ± 1·24	0·912	0·006	<0·001
Rectum	D_{2cc} (Gy)	11·74 ± 3·28	13·95 ± 2·51	20·42 ± 1·30	0·075	<0·001	<0·001
Sigmoid	D_{2cc} (Gy)	14·03 ± 5·04	12·78 ± 6·07	16·47 ± 7·30	1·000	0·237	0·101
Femoral head (L)	D_{2cc} (Gy)	2·74 ± 0·42	5·09 ± 1·58	10·11 ± 1·80	0·002	<0·001	<0·001
Femoral head (R)	D_{2cc} (Gy)	2·77 ± 0·61	4·54 ± 1·72	8·85 ± 1·57	0·009	<0·001	<0·001

[a]IBT boost versus AG-VMAT boost.
[b]IBT boost versus VMAT boost.
[c]VMAT boost versus AG-VMAT boost.
Abbreviations: OAR, organ at risk; SD, standard deviation; IBT, intracavitary brachytherapy; AG-VMAT, applicator-guided volumetric modulated arc therapy; $D_{90,}$ dose received by 90% of the target; CI, conformity index; HI, homogeneity index; D_{2cc}; minimum doses of the most exposed 2 cm^3 volume of the OAR; EBRT, external beam radiotherapy; EQD_2, minimum doses of the most exposed 2 cm^3 volume of the OAR.

Table 5. Comparison of cumulative equivalent dose in 2 Gy per fraction (EQD_2) for target and organ at risk (OAR) between external beam radiotherapy (EBRT) + intracavitary brachytherapy boost, EBRT + applicator-guided volumetric modulated arc therapy (AG-VMAT) boost, and EBRT + VMAT boost using constraint set by American Brachytherapy Society (ABS)[20]

Parameter		Cumulative EQD_2 (Gy)			
		EBRT + IBT boost (Mean ± SD)	EBRT + AG-VMAT boost (Mean ± SD)	EBRT + VMAT boost (Mean ± SD)	Constraint set by ABS
D_{90}	Target	80·53 ± 2·76	65·35 ± 1·48	65·10 ± 1·26	80–90
D_{2cc}	Bladder	72·14 ± 17·02	57·90 ± 3·87	64·18 ± 2·29	≤90
	Rectum	61·60 ± 7·36	56·26 ± 3·02	64·26 ± 1·91	≤75
	Sigmoid	68·42 ± 13·92	55·49 ± 5·75	59·88 ± 8·17	≤75

Dosimetry analysis of tumour target and OAR in IBT, AG-VMAT, and VMAT boosts

The dose to target tumour and OAR between IBT, AG-VMAT, and VMAT boosts was compared, as shown in Table 4. In terms of target coverage, the study found that the D90 and HI of the target in the IBT boost were significantly higher than those in the AG-VMAT boost (p-value = 0·023 and <0·001) and VMAT (p-value = 0·034 and <0·001) boosts. The D90 of the target dose showed no significant difference (p-value = 0·897) between the AG-VMAT and VMAT boosts, but the HI in the VMAT boost was significantly higher than the AG-VMAT boost (p-value = 0·009). Regarding the CI of the target, the results indicated a significant difference between the IBT and AG-VMAT boosts.

While assessing the OAR dose, the D_{2cc} of the bladder, rectum and both femoral heads in the VMAT boost was in significantly higher doses than the IBT boost and AG-VMAT boost. Nevertheless, there were no significant differences in D_{2cc} doses for the bladder (p-value = 0·912), rectum (p-value = 0·075) and sigmoid (p-value = 1·000) between the IBT boost and AG-VMAT boost. The D_{2cc} of the left (p-value = 0·002) and right femoral heads (p-value = 0·009) in the AG-VMAT boost were significantly higher than that in the IBT boost.

In terms of EQD_2, as shown in Table 5, the cumulative EQD_2 for D_{90} of the target tumour in the IBT boost fell within the dose constraint. However, the mean D_{90} in the AG-VMAT boost and VMAT boost were 65·35 Gy and 65·10 Gy, respectively, which failed to meet the recommended dose range of 80–90 Gy EQD_2. For OAR, D_{2cc} for all the OAR doses in the IBT, VMAT and AG-VMAT boosts fell within the EQD_2 constraint set by the ABS.

Dosimetric evaluation for different hypofractionation schemes of AG-VMAT boosts

Table 6 represents the evaluation of cumulative EQD_2 between different hypofractionation schemes of AG-VMAT boost. Among the six hypofractionation schemes, only the cumulative EQD_2 for D_{90} of the target (PTV) dose in 24 Gy/3 fractions (mean: 81·81 Gy) and 25·5 Gy/3 fractions (mean: 84·88 Gy) fell within the tolerance limit of 80–90 Gy EQD_2. As for OAR, the cumulative EQD_2 for D_{2cc} of the bladder, sigmoid and rectum in all hypofractionation schemes were within the tolerance limit set by ABS, except for the D_{2cc} of the rectum in 25·5 Gy/3 fraction. In short, a dose prescription of 24 Gy/3 fractions for AG-VMAT boost technique achieved the target and OAR dose within the ABS tolerance limit.

Discussion

The current study was undertaken to mimic the pear-shaped distribution of the IBT boost in the AG-VMAT boost. Pear-shaped distribution of IBT boost is crucial in the treatment of locally advanced cervical cancer because it includes the cervix, uterus and vagina, promoting a heterogenous dose distribution that spares the nearby OAR. However, the CTV in the VMAT boost only includes

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Table 6. Evaluation of cumulative equivalent dose in 2 Gy per fraction (EQD_2) between different hypofractionation schemes of applicator-guided volumetric modulated arc therapy (AG-VMAT) boost using dose constraint set by American Brachytherapy Society (ABS)

		Cumulative EQD_2 (Gy) for EBRT + different hypofractionation schemes of AG-VMAT boost						
Parameter	OAR	20 Gy/5 fx (Mean ± SD)	25 Gy/5 fx (Mean ± SD)	20 Gy/4 fx (Mean ± SD)	19·5 Gy/3 fx (Mean ± SD)	24 Gy/3 fx (Mean ± SD)	25·5 Gy/3 fx (Mean ± SD)	EQD_2 constraint set by ABS (Gy)
D_{90}	Target	68·79 ± 1·46	76·76 ± 1·21	70·48 ± 1·52	72·46 ± 1·40	81·81 ± 1·57	84·88 ± 2·03	80–90
D_{2cc}	Bladder	62·26 ± 6·00	69·86 ± 8·65	64·48 ± 6·99	67·80 ± 8·73	77·60 ± 11·80	81·00 ± 13·09	≤90
	Rectum	60·60 ± 3·65	66·82 ± 6·11	62·51 ± 4·50	65·02 ± 5·57	73·28 ± 8·29	76·08 ± 9·29	≤75
	Sigmoid	56·89 ± 8·25	62·15 ± 12·08	58·46 ± 9·49	60·48 ± 11·42	67·03 ± 16·28	69·11 ± 18·10	≤75

the gross tumour volume and the entire cervix.[21] This allows a more homogeneous dose distribution around the target volume, which is inferior to a boost treatment.[7]

Table 4 shows that the D_{90} of the target was significantly better and in favour of the IBT boost. The result followed the study done by Khosla et al.,[16] Pinzi et al.,[22] and Hegazy et al.,[17] but in contrast with the findings by Dobelbower et al.[23] and Wali et al.[24] who reported a superior target coverage in the VMAT boost compared to the IBT boost. This advantage in the IBT boost was attributed to the heterogeneity within the target volume, as evidenced by the significant increase in the HI. This unique characteristic allowed the IBT boost to deliver a high central dose to the target volume and hypoxic cells while sparing nearby OARs, thus a better LC.[15] Meanwhile, both VMAT and AG-VMAT boosts had a more homogenous dose distribution as their HI value was closer to 0. On the other hand, the CI difference between the three boost techniques was due to the small sample size and planning factors.[25]

In assessing the OAR sparing, the VMAT boost demonstrated the poorest OAR sparing as indicated by the significant increases in the D2cc dose for all OARs compared to the IBT and AG-VMAT boosts, except for the sigmoid. This was because it did not involve the insertion of the applicator and gauze packing of the vagina that displaces OAR.[26] Nevertheless, the D_{2cc} dose for the bladder, rectum and sigmoid in IBT and AG-VMAT boosts were comparable because they were planned to use the same CT images where the patient's anatomy and position were the same. The findings complied with the study done by Georg et al.[27] but contrasted with the study performed by Wali et al.[24] who found that the AG-VMAT boost had caused significant reductions to D_{2cc} doses for the bladder and rectum compared to the IBT boost. Furthermore, this study highlighted significant increments in the D_{2cc} dose to both femoral heads' doses in the VMAT and AG-VMAT boosts in comparison to the IBT boost. This was because these two VMAT boost techniques exposed surrounding normal tissues to more low-dose radiation, leading to a potential risk of having a secondary malignancy.[7] The result was supported by the findings from Sethi et al.,[28] Merrow et al.[29] and Wali et al..[24]

In short, the IBT boost achieved the best target coverage and provided better OAR sparing. VMAT boost showed inferior target coverage and the poorest OAR sparing. This signified the importance of this research to help the VMAT boost reproduce the dosimetry as in the IBT boost by duplicating the pear-shaped distribution in the AG-VMAT boost. However, the AG-VMAT boost still had inferior target coverage but had achieved similar OAR sparing as in the IBT boost, except for higher doses to the femoral heads. Although a pear-shaped PTV had been created in AG-VMAT boost, the reproducibility of dose distribution remained undetermined and must be confirmed by performing EQD_2 calculation.

According to Table 5, only the D_{90} dose of the target and the D_{2cc} dose of the OAR in the IBT boost were within the recommended tolerance limit by ABS. Meanwhile, the cumulative EQD_2 for D_{90} dose of PTV in VMAT and AG-VMAT boosts did not fall within the tolerance limit although their OAR doses were within the ABS limit. The result of the current study was inconsistent with the study conducted Pinzi et al.[22] in which the cumulative EQD_2 for the D_{90} dose of the target in the IBT boost was similar to IMRT boost and both boost techniques did not meet the tolerance limit. However, the result of the current study aligned with Khosla et al.[16] who found that the cumulative EQD_2 for D_{2cc} of bladder and rectum in both IBT boost and IMRT boost was within the dose constraint suggested by ABS.

The IBT boost practised at our institution was able to provide sufficient target coverage and OAR sparing. Nevertheless, the target doses in both AG-VMAT and VMAT boosts were not achievable to reproduce the dosimetry of the IBT boost, which was within 80–90 Gy EQD_2. This was due to the different dose fractionation schemes in IBT (18 Gy/2 fractions, 21Gy/3 fractions, or 22·5 Gy/3 fractions), AG-VMAT (20 Gy/10 fractions), and VMAT boost even though they had the same total prescription dose. The smaller dose fractionation in AG-VMAT and VMAT boosts resulted in a significant EQD_2 reduction.[30,31] Hence, we concluded that the 20 Gy/10 fraction prescription dose for VMAT and AG-VMAT boosts at our institution was insufficient to provide good target coverage. Thus, the prescription dose for the VMAT boost treatment delivery at our institution should be changed to a hypofractionated regimen.

To identify a new prescription dose for VMAT and AG-VMAT boost, six different hypofractionation schemes were applied to see which dose fractionation could reproduce the target coverage of the IBT boost while maintaining the OAR sparing. Table 6 showed that only the cumulative EQD_2 for D_{90} of the target and D_{2cc} of all the OAR doses in 24 Gy/3 fractions AG-VMAT boost complied with the dose constraint set by ABS. Thus, the 24 Gy/3 fractions AG-VMAT boost reproduced the pear-shaped distribution as in the IBT boost.

AG-VMAT boost with 24 Gy/3 fraction used an ultra-hypofractionation scheme which was believed to significantly lessen the sublethal damage repair in the tumour, leading to a reduction in tumour repopulation, thus better tumour control. Nevertheless, the large dose fractionation might worsen the late toxicity and radiobiological effect on surrounding normal tissues and toxicity rates.[32] For example, Albuquerque et al.[33] reported a high rate of late toxicity (26·7%) and a lower 70% LC rate using ultra-hypofractionation schemes of SBRT boost in locally advanced cervical cancer. Furthermore, the ultra-hypofractionation caused a larger reduction in the redistribution and reoxygenation of the tumour, which may eventually reduce the efficacy of the treatment.[34] In the 24 Gy/3

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fractions treatment, the reoxygenation utilisation rates were only 66%, which were lower than 75% and 80% in the 4 and 5-fraction treatments, respectively. Hence, for better reoxygenation, the interfraction intervals of at least 3–7 days may be applied in 24 Gy/3 fractions of AG-VMAT boost.[11,35] Given the biological effects, further research is needed to validate the application of the 24 Gy/3 fractions AG-VMAT boost in clinical settings.

There were several limitations in this study. Firstly, the target delineation in the IBT boost was a key issue. Most of the previously published studies followed the GEC ESTRO recommendations for HR-CTV delineation.[17,24] However, in this study, HR-CTV was defined using the 100% isodose line in the IBT boost, which was not accurate. Moreover, the dose was prescribed to point A instead of HR-CTV in this study. This was detrimental as point A did not correspond to specific anatomical structures, leading to uncertainty in target coverage.[36] Thirdly, the small sample size and lack of clinical follow-up data, especially for the application of different hypofractionation schemes were also one of the limitations. Additionally, the AG-VMAT boost was planned to use an IBT CT image to maintain consistent contours, rather than using two separate patient groups. This meant that the AG-VMAT boost treatment plan was always virtual and the patient's anatomy and position were not the same as those used for VMAT boost. Lastly, the LQ model was inappropriate for quantitative predictions of dose fractionation as the LQ model might overestimate the biological effect of the dose per fraction exceeding 6 Gy.[37]

Future research should focus on the radiobiological evaluation of 24 Gy/3 fractions VMAT boost. Furthermore, comparisons between both IBT and VMAT boost techniques should not only address dosimetry but also consider logistic, clinical, and quality assurance comparisons. Despite these limitations, this study provides valuable data on the dosimetry difference between IBT boost and VMAT boost. It also provides significant data on the potential of VMAT boost to replace the IBT boost in locally advanced cervical cancer as this study had successfully reproduced the pear-shaped distribution.

Conclusion

The pear-shaped outline was successfully reproduced in the AG-VMAT boost by using the 100% isodose line from the IBT boost. However, both AG-VMAT and VMAT boosts failed to replicate the dosimetry of the IBT boost in terms of target coverage due to the insufficient prescription dose. Hypofractionation implemented for AG-VMAT boost using 24 Gy/3 fraction was able to reproduce the dosimetry in IBT boost by providing sufficient target coverage and OAR sparing. However, further research is needed to validate the application of a 24 Gy/3 fractions of VMAT boost in clinical settings.

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References

1. World Health Organization. Cervical Cancer. Geneva: WHO; 2022.
2. NCCN. NCCN Clinical Practice Guideline in Oncology Cervical Cancer. Plymouth Meeting, PA: NCCN; 2019.
3. Campitelli M, Lazzari R, Piccolo F, et al. Brachytherapy or external beam radiotherapy as a boost in locally advanced cervical cancer: a gynaecology study group in the Italian association of radiation and clinical oncology (AIRO) review. Int J Gynecol Cancer 2021; 31 (9): 1278–1286.
4. Han K, Milosevic M, Fyles A, Pintilie M, Viswanathan AN. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 2013; 87 (1): 111–119.
5. Korenaga TRK, Yoshida EJ, Pierson W, et al. Better late than never: brachytherapy is more important than timing in treatment of locally advanced cervical cancer. Gynecol Oncol 2022; 164 (2): 348–356.
6. Mahmoud O, Kilic S, Khan AJ, Beriwal S, Small W. External beam techniques to boost cervical cancer when brachytherapy is not an option-theories and applications. Ann Transl Med 2017; 5 (10): 207.
7. Al Feghali KA, Elshaikh MA. Why brachytherapy boost is the treatment of choice for most women with locally advanced cervical carcinoma? Brachytherapy 2016; 15 (2): 191–199.
8. Viswanathan AN, Moughan J, Small WJ, et al. The quality of cervical cancer brachytherapy implantation and the impact on local recurrence and disease-free survival in radiation therapy oncology group prospective trials 0116 and 0128. Int J Gynecol Cancer 2012; 22 (1): 123–131.
9. Kirchheiner K, Nout RA, Czajka-Pepl A, et al. Health related quality of life and patient reported symptoms before and during definitive radio(chemo) therapy using image-guided adaptive brachytherapy for locally advanced cervical cancer and early recovery - a mono-institutional prospective study. Gynecol Oncol 2015; 136 (3): 415–423.
10. Rashid A, Ahmad Z, Memon MA, Hashim ASM. Volumetric modulated arc therapy (VMAT): a modern radiotherapy technique - a single institutional experience. Pak J Med Sci 2021; 37 (2): 355–361.
11. Tanderup K, Fokdal LU, Sturdza A, et al. Effect of tumor dose, volume and overall treatment time on local control after radiochemotherapy including MRI guided brachytherapy of locally advanced cervical cancer. Radiother Oncol 2016; 120 (3): 441–446.
12. Teoh M, Clark CH, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. Br J Radiol 2011; 84 (1007): 967–996.
13. Assenholt MS, Petersen JB, Nielsen SK, Lindegaard JC, Tanderup K. A dose planning study on applicator guided stereotactic IMRT boost in combination with 3D MRI based brachytherapy in locally advanced cervical cancer. Acta Oncol (Madr) 2008; 47 (7): 1337–1343.
14. Pedicini P, Strigari L, Caivano R, et al. Local tumor control probability to evaluate an applicator-guided volumetric-modulated arc therapy solution as alternative of 3D brachytherapy for the treatment of the vaginal vault in patients affected by gynecological cancer. J Appl Clin Med Phys 2013; 14 (2): 4075.
15. Sharma DN, Gandhi AK, Sharma S, Rath GK, Jagadesan P, Julka PK. Interstitial brachytherapy vs. intensity-modulated radiation therapy for patients with cervical carcinoma not suitable for intracavitary radiation therapy. Brachytherapy 2013; 12 (4): 311–316.
16. Khosla D, Patel FD, Oinam AS, Tomar P, Sharma SC. Dosimetric comparison of vaginal vault ovoid brachytherapy versus intensity-modulated radiation therapy plans in postoperative patients of cervical carcinoma following whole pelvic radiotherapy. J Cancer Res Ther 2014; 10 (1): 153–158.
17. Hegazy H, Hegazy N, Soliman M, Elsaid A. Dosimetric comparison between high dose rate brachytherapy boost and volumetric arc therapy boost in locally advanced cancer cervix. Asian J Oncol 2021; 07 (02): 085–088.
18. Matsukawa H, Sasaki T, Hirayama R, Hirose TA, Fukunaga JI. Assessment of the anatomical position of point B and the relationship between point B dose and the dose delivered to pelvic lymph nodes in CT-based high-dose-rate brachytherapy for uterine cervical cancer. J Contemp Brachytherapy 2019; 11 (2): 137–145.

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19. Bisello S, Cilla S, Benini A, et al. Dose–volume constraints fOr oRganS at risk In radiotherapy (CORSAIR): an "all-in-one" multicenter–multidisciplinary practical summary. Curr Oncol 2022; 29 (10): 7021–7050.
20. Georg P, Kirisits C, Goldner G, et al. Correlation of dose-volume parameters, endoscopic and clinical rectal side effects in cervix cancer patients treated with definitive radiotherapy including MRI-based brachytherapy. Radiat Oncol 2009; 91 (2): 173–180.
21. Lee TH, Song C, Kim IA, et al. Stereotactic ablative body radiotherapy boost for cervical cancer when brachytherapy boost is not feasible. Radiat Oncol 2021; 16 (1): 1–11.
22. Pinzi V, Landoni V, Cattani F, Lazzari R, Jereczek-fossa BA, Orecchia R. IMRT and brachytherapy comparison in gynaecological cancer treatment: thinking over dosimetry and radiobiology. ecancer 2019; 13:993.
23. Dobelbower MC, Shen S, Popple R, Kim RY. Dosimetric comparison of IMRT to HDR intracavitary brachytherapy for cervical cancer. Brachytherapy 2007; 6 (2): 84.
24. Wali L, Helal A, Darwesh R, Attar M. A dosimetric comparison of volumetric modulated arc therapy (VMAT) and high dose rate (HDR) brachytherapy in localized cervical cancer radiotherapy. J Xray Sci Technol 2019; 27 (3): 473–483.
25. Brennan SM, Thirion P, Buckney S, Shea CO, Armstrong J. Factors influencing conformity index in radiotherapy for non-small cell lung cancer. Med Dosim 2010; 35 (1): 38–42.
26. Sud S, Roth T, Jones E. Clinical analysis of speculum-based vaginal packing for high-dose-rate intracavitary tandem and ovoid brachytherapy in cervical cancer. J Contemp Brachytherapy 2018; 10 (1): 32–39.
27. Georg D, Kirisits C, Hillbrand M, Dimopoulos J, Pötter R. Image-guided radiotherapy for cervix cancer: high-tech external beam therapy versus high-tech brachytherapy. Int J Radiat Oncol Biol Phys 2008; 71 (4): 1272–1278.
28. Sethi RA, Jozsef G, Grew D, et al. Is there a role for an external beam boost in cervical cancer radiotherapy? Front Oncol 2013; 3:1–6.
29. Merrow C, deBoer S, Podgorsak MB. VMAT for the treatment of gynecologic malignancies for patients unable to receive HDR brachytherapy. J Appl Clin Med Phys 2014; 15 (5): 66–73.
30. Wang JZ, Li XA, D'Souza WD, Stewart RD. Impact of prolonged fraction delivery times on tumor control: a note of caution for intensity-modulated radiation therapy (IMRT). Int J Radiat Oncol Biol Phys 2003; 57 (2): 543–552.
31. Shaikh M, Burmeister J, Joiner M, Pandya S, Zhao B, Liu Q. Biological effect of different IMRT delivery techniques: SMLC, DMLC, and helical tomotherapy. Med Phys 2010; 37 (2): 762–770.
32. Small WJ, Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys 2008; 71 (2): 428–434.
33. Albuquerque K, Tumati V, Lea J, et al. A phase II trial of stereotactic ablative radiation therapy as a boost for locally advanced cervical cancer. Int J Radiat Oncol Biol Phys 2020; 106 (3): 464–471.
34. Brand DH, Kirby AM, Yarnold JR, Somaiah N. How low can you go? The radiobiology of hypofractionation. Clin Oncol 2022; 34 (5): 280–287.
35. Shibamoto Y, Miyakawa A, Otsuka S, Iwata H. Radiobiology of hypofractionated stereotactic radiotherapy: what are the optimal fractionation schedules? J Radiat Res 2016; 57: i76–i82.
36. Kehwar T, Goyal M. High dose rate brachytherapy of carcinoma of the cervix: applicability of various dosimetry systems and guidelines in the dose prescription and treatment planning. na J Radiat Oncol Cancer 2016; 2 (1): 1015.
37. Tornero-López AM, Guirado D. Radiobiological considerations in combining doses from external beam radiotherapy and brachytherapy for cervical cancer. Rep Pract Oncol Radiother 2018; 23 (6): 562–573.

https://doi.org/10.1017/S1460396924000311 Published online by Cambridge University Press