Journal of Nuclear Medicine & Radiation Therapy

Lapuz et al., J Nucl Med Radiat Ther 2019, 10:3

Research Article Open Access

The Impact of Planning Target Volume Margins on Four-Field Pelvic Radiotherapy, Intensity Modulated Radiotherapy and Volumetric Modulated Arc Therapy in Cervical Cancer: A Dosimetric Comparison

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Received date: May 21, 2019; **Accepted date:** June 25, 2019; **Published date:** July 03, 2019

Abstract

Objective: To compare conventional Four-Field Pelvic Radiotherapy (4FRT), Intensity Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) in cervical cancer using increasing Clinical Target Volume (CTV) to Planning Target Volume (PTV) margins to account for daily variability in uterine position and to assess whether dosimetric advantages with advanced planning techniques continue with larger PTV margins.

Methods: Twenty patients with locally advanced cervical cancer previously treated with definitive radiation therapy were selected for the study. For each patient, computed tomography planning scans were obtained and PTVs were created with CTV to PTV uterine margins of 1.5 cm, 2 cm, 2.5 cm and 3 cm if anatomically feasible. 4FRT, IMRT and VMAT plans were generated and evaluated for target coverage, conformity, and homogeneity, dose to Organs at Risk (OAR), Total Monitor Units (MU) and delivery time.

Results: A total of 136 plans were generated. Target coverage was excellent for all plans generated regardless of technique. VMAT and IMRT were associated with significantly reduced dose to OAR compared with 4FRT for all CTV to PTV uterine margins ($p \leq 0.05$). VMAT plans were associated with lower rectum V40 ($p \leq 0.02$) and bowel V40 ($p \leq 0.04$) for the smaller uterine margins and lower MU and delivery time ($p \leq 0.01$).

Conclusion: VMAT and IMRT result in significantly lower doses to OAR compared with 4FRT in cervical cancer, regardless of CTV to PTV margins used to account for uterine motion. VMAT was associated with shorter delivery times compared with IMRT, which is useful in cervical cancer radiation therapy where intrafraction uterine motion may result in target under coverage if inadequate uterine margins are used. Accurate localization of the uterus with daily image guidance is critical when considering these advanced planning techniques for definitive radiation therapy in cervical cancer.

Keywords Cervical cancer; Radiotherapy; External beam radiotherapy; IMRT; VMAT; 3DCRT; Organs at risk

Introduction

The current standard treatment for locally advanced cervical cancer is definitive whole pelvis External Beam Radiotherapy (EBRT) with concurrent cisplatin-based chemotherapy followed by brachytherapy [1]. Traditionally, Four-Field Pelvic Radiotherapy (4FRT) has been used, resulting in a boxed shape distribution to cover the primary tumor, remaining cervix, uterus, upper vagina, parametria and pelvic lymph nodes. However, this technique includes a substantial amount of normal tissue within the radiotherapy fields. It is associated with considerable acute and long term toxicities and up to 25% of women experience grade 3-4 gastrointestinal and genitourinary toxicities [2].

Modern radiotherapy techniques including Intensity Modulated Radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT) have the potential benefits of conforming dose to the target whilst reducing dose to Organs at Risk (OAR) [3-5]. Published literature in cervical cancer suggests a dosimetric benefit in using these modern techniques [6-8], and emerging evidence suggests this translates to a clinical benefit, although longer term follow-up is awaited [9-11]. Nevertheless, IMRT and VMAT use in cervical cancer is guarded due to the large inter-patient and intra-patient variation in uterine motion and the concern about geographical miss [1,12]. The improvements in Image-Guided Radiation Therapy (IGRT) have allowed direct visualization of treatment volumes before radiation delivery each day, reducing target uncertainty. In addition, generous Planning Target Volume (PTV) margins can be applied to encompass the extent of uterine motion [13].

However, if larger PTV margins are required to account for uterine motion, there may be minimal benefit, if any, with these modern techniques over 4FRT [14,15]. The aims of this study are: (1) to report a dosimetric comparison of 4FRT, IMRT and VMAT in patients with locally advanced cervical cancer, and (2) to assess whether any dosimetric differences found persist with the use of larger geometric margins to account for daily variability in uterine position.

Material and Methods

Patient selection criteria

The Computed Tomography (CT) planning data sets of 20 consecutive patients with locally advanced cervical cancer, previously treated with definitive EBRT between August 2012 and August 2014 at the Calvary Mater Newcastle, New South Wales, Australia, were used for this study. All patients were simulated and treated in the supine position with a full bladder and empty rectum as per departmental protocol. Baseline patient and tumor characteristics were recorded including age, International Federation of Gynecology and Obstetrics (FIGO) stage, histology, pre-treatment imaging with Magnetic Resonance Imaging (MRI) and/or Positron Emission Tomography (PET), tumor size, lymph node involvement, uterine invasion and chemotherapy details.

Contouring

Volumes were contoured by one radiation oncologist and verified by a second radiation oncologist. The Gross Tumor Volume (GTV) was defined as the gross tumor and any vaginal or uterine involvement based on examination under anesthesia findings, CT, MRI and PET. Clinical target volume (CTV) was defined as the GTV and potential microscopic disease including the remaining cervix (if not included in the GTV), uterus, upper vagina, parametrium, ovaries and regional lymph nodes. Structures were contoured based on published guidelines [16-19].

The following separate structures were contoured to allow for differential PTV margin expansion: primary tumor CTV (CTV-T) which consists of the GTV and cervix if not already included in the GTV; uterine CTV (CTV-U) which consists of the entire uterus; parametrial and vaginal CTV (CTV-P) which includes the parametrium, parauterine fat, ovaries, paravaginal tissues and proximal vagina; and nodal CTV (CTV-N) which consists of nodal regions at risk, including external and internal iliac, presacral and obturator nodes. The primary PTV (PTV-T) was generated with a 1.5 cm uniform expansion on CTV-T. Parametrical/Vaginal PTV (PTV-P) was generated with a 1cm uniform expansion on CTV-P.

Nodal PTV (PTV-N) was generated with a 0.7 cm uniform expansion on CTV-N [19]. For uterine PTV (PTV-U), recommended CTV to PTV margins can differ significantly in literature depending on methodology used to assess uterine motion and can range from 1.5 cm to 4 cm [16,20]. Therefore, to account for this variability in uterine motion, increasing geometric margins for the uterus were used. Six PTV-Us were created for each patient using 1.5, 2, 2.5, 3, 3.5 and 4 cm uniform expansions on CTV-U. Each final PTV was created by combining PTV-T, PTV-P, PTV-N and one PTV-U to generate six PTVs for each patient: PTV1.5, PTV2, PTV2.5, PTV3, PTV3.5 and PTV4 based on 1.5, 2, 2.5, 3, 3.5 and 4 cm uterine margins respectively. The rectum, bladder, bowel and femoral heads were delineated as OAR and contoured as solid structures. The rectum was defined as the outer rectal wall from the recto sigmoid junction superiorly to the anus inferiorly at the lowest level of the ischial tuberosities. The bladder was defined as the outer bladder wall from the base inferiorly to the dome superiorly.

The bowel was contoured as a bowel bag defined as loops of bowel (small or large bowel) and surrounding volume to the edge of the peritoneum from 1 cm above the PTV superiorly to the most inferior small or large bowel loop. Left and right femoral heads were defined as the entire femoral head, excluding the femoral neck.

Treatment planning

All plans were calculated using the Anisotropic Analytical Algorithm (AAA Version 11.0.31) using Eclipse External Beam Planning v11.0 (Varian Medical Systems, Palo Alto, SA). For each patient, one 4FRT plan was generated as per department protocol using a co-planar, four-field static 18 MV photon beam arrangement, with gantry angles of 0°, 90°, 180° and 270°. Shielding was obtained using a Millennium 120 leaf collimator with 0.5 cm leaves and was based on conventional field borders ensuring coverage of PTV1.5. The dose rate for each beam was 600 Monitor Units (MU) per minute. IMRT and VMAT plans were generated for each PTV, except when the PTV extended outside 4FRT field borders due to excessive uterine margins for the patient's anatomy and these PTVs were excluded from the study.

For IMRT planning, a co-planar, nine field 6MV photon beam arrangement was used, with gantry angles of 20°, 40°, 80°, 120°, 180°, 240°, 280°, 320° and 340°. The dose rate of these beams was 400 MU per minute. Dose was prescribed to the PTV. For VMAT planning, two 6MV photon arcs were used. The first arc had a gantry starting angle of 18° and moved clockwise to 179°, whilst the second arc had a gantry start angle of 179° and moved counter-clockwise to 181°. The dose rate for both arcs was 600 MU per minute. Dose was prescribed to the PTV. The radiotherapy dose prescription was 45 Gy in 25 fractions.

Target planning objectives were: (1) dose to 99% of the PTV was at least 95% of the prescribed dose (D99 ≥ 42.75 Gy), (2) minimum dose to hottest 1% of the PTV was less than 107% (D<48.15 Gy) and (3) maximum point dose was less than 50 Gy. For the IMRT and VMAT plans, dose constraints on OAR were used to optimize dose distribution without compromising the target volume. OAR dose constraints were: (1) bowel - volume receiving at least 45 Gy (V45) was less than 200 cc and maximum dose was less than 50 Gy, (2) rectum- V45<50% and maximum dose less than 50 Gy, (3) bladder - V45<50% and maximum dose less than 50 Gy, and (4) femoral heads - volume receiving at least 30 Gy (V30) was less than 15% and maximum dose less than 50 Gy.

Once PTV dose coverage had been achieved, the highest priorities for dose constraints were typically placed on the rectum and bowel, followed by the bladder and femoral heads. A dose-tuning ring around the PTV was also used to aid in increasing the dose gradient between the PTV and normal tissue. All treatment plans were generated by two radiation therapists, results checked by a third radiation therapist and reviewed by a radiation oncologist.

Plan evaluation

Plans were evaluated for PTV coverage, conformity, and dose homogeneity, dose to OAR (bowel, rectum, bladder and femoral heads), total MU and estimated delivery time. The 4FRT plan for each

patient was used to assess dosimetric parameters for all PTVs (PTV1.5 to PTV3) generated for that patient. PTV dosimetric parameters evaluated were V45 and V42.75 (volume receiving at least 45 Gy and 42.75 Gy) and D99, D97 and D1 (minimum dose (Gy) received by the hottest 99%, 97% and 1% of the PTV).

OAR dosimetric parameters evaluated were bowel, rectum and bladder V45 and V40 (volume receiving at least 40 Gy) and femoral head V45 and V30. Conformity was assessed using the Radiation Therapy Oncology Group (RTOG) Conformity Index (CIRTOG) and Conformation Number (CN) defined as follows:

$$CI_{RTOG} = \frac{V(100\%\ \ iso)}{V(PTV)}$$

$$CN = \frac{PTV\ \ V45}{V(PTV)} \times \frac{PTV\ \ V45}{V(100\%\ \ iso)}$$

Where, V (100% iso) is the total volume (cc) of the 100% isodose, V (PTV) is the total volume (cc) of the PTV and PTV V45 is the volume (cc) of the PTV receiving at least 45 Gy [21,22]. CIRTOG and CN closer to 1 are associated with better conformity. Homogeneity was calculated using the Homogeneity Index (HI) recommended by the International Commission on Radiation Units and Measurements (ICRU):

$$HI = \frac{D2 - D98}{D50}$$

Where, D2, D50 and D98 are the minimum dose to the hottest 2%, 50% and 98% of the PTV respectively [23]. HI closer to zero is associated with better homogeneity. Estimated treatment delivery times were calculated as follows: Each plan was delivered in an empty treatment bunker using a Varian Trilogy Linear Accelerator (Varian Medical Systems, Palo Alto, CA). A stopwatch was used to time the delivery, and was started at the "beam on" for the first treatment beam, and stopped after the final treatment beam was delivered. A second stopwatch was used as a backup in case the first stopwatch failed. Planning times were recorded for the last ten patients due to the anticipated longer planning times for the earlier patients whilst building planning proficiency. However, they were not included in the comparative statistical analysis.

Statistical analysis

Descriptive statistics were obtained for all parameters. The three radiotherapy techniques were compared using a mixed effects regression model, a random intercept to model the repeated measures. P-values from the F-test of the technique fixed effect are presented together with means and standard deviations. P-values less than 0.05 were indicative of a difference between radiotherapy techniques. Firstly, comparison was conducted between the three radiotherapy techniques within each uterine PTV margin. Post-hoc paired comparisons were conducted to identify which radiotherapy techniques differed. Finally, comparison of differences between radiotherapy techniques was conducted between the uterine margins. All statistical analyses were programmed using SAS v9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Patient characteristics

The median patient age was 56 years (range: 27-84 years). FIGO stage 2B was the most common stage. A total of 15 patients (75%) had squamous cell carcinomas on cervical biopsy. All patients had diagnostic PET scans with most having MRI scans (n=19). Nodal and uterine involvement was seen in 13 and 15 patients respectively. Median tumor size was 5.1 cm (range: 1.5-8.3 cm). Most patients (n=18.90%) had concurrent chemotherapy. The patient and tumor characteristics are summarized in Table 1.

Characteristic	No.	%
Age (years)		
Median (range)	56 (27-84)	
FIGO stage		
1B	1	5%
2A	3	15%
2B	9	45%
3B	4	20%
4A	3	15%
Histology		
Squamous cell carcinoma	15	75%
Adenocarcinoma	5	25%
Tumor size (cm)		
Median (range)	5.1 (1.5-8.3)	
Diagnostic imaging		
PET	20	100%
MRI	19	95%
Nodal involvement		
Yes	13	65%
No	7	35%
Uterine involvement		
Yes	15	75%
No	5	25%
Concurrent chemotherapy		
Yes	18	90%
No	2	10%

Table 1: Patient and tumor characteristics.

PTV evaluation

PTV2.5, PTV3, PTV3.5 and PTV4 extended outside the 4FRT fields in 9 (45%), 13 (65%), 20 (100%) and 20 (100%) patients respectively and therefore IMRT and VMAT plans were not created for these PTVs. A total of 136 plans were generated (20 4FRT, 58 IMRT and 58 VMAT plans). Mean and standard deviations for the evaluated parameters for all plans are shown for PTV1.5 (Table 2), PTV2 (Table 3), PTV2.5 (Table 4) and PTV3 (Table 5). Evaluation of radiotherapy techniques was carried out for 20 patients for PTV1.5 (Table 2), 20 patients for

PTV2 (Table 3), 11 patients for PTV2.5 (Table 4) and 7 patients for PTV3 (Table 5). The PTV planning objectives were achieved for all plans with all techniques. For PTV V42.75, there was a statistically significant difference between techniques (p<0.01), with significantly higher V42.75 seen with 4FRT and VMAT than with IMRT on paired comparisons for all uterine margins (p<0.01 and p 0.04 respectively). Significantly higher PTV V42.75 was seen with 4FRT compared with VMAT on paired comparisons for PTV1.5, PTV2 and PTV2.5 (p 0.02) but was not significant for PTV3 (p=0.09). PTV coverage was excellent with a mean PTV V42.75 of at least 99% for all techniques and for all uterine margins (PTV1.5, PTV2, PTV2.5, PTV3) (Tables 2-5). There was a statistically significant difference in PTV D97 (p=0.04) for PTV1.5, with 4FRT being higher than VMAT on paired comparison. For uterine margins of 2-3 cm, there was no significant difference in PTV D97 between techniques. PTV D1 was statistically significantly different between techniques for all uterine margins (p<0.01). On paired comparison, PTV D1 was higher with IMRT than either 4FRT (p<0.01) or VMAT (p<0.01) for all uterine margins. There was no significant difference between 4FRT and VMAT for the various uterine margins except for PTV2 (p=0.03). Mean PTV D1 was 46.8 Gy to 47.6 Gy for all techniques (i.e. 104%-106% of prescription dose), such that any statistically significant differences seen on analysis would not be clinically significant.

Variables	4FRT	IMRT	VMAT	Overall technique comparison	4FRT *vs* IMRT	4FRT *vs* VMAT	IMRT *vs* VMAT
	(n=20)	(n=20)	(n=20)	p value	p value	p value	p value
	mean (sd)	mean (sd)	mean (sd)				
PTV							
V45 (%)	82.6 (9.1)	91.7 (3.4)	80.1 (7.6)	<0.01	<0.01	0.26	<0.01
V42.75 (%)	99.8 (0.4)	99.1 (0.1)	99.5 (0.3)	<0.01	<0.01	0.01	<0.01
D99 (Gy)	43.5 (0.6)	42.8 (0.1)	43.2 (0.3)	<0.01	<0.01	0.02	0.01
D97 (Gy)	44.1 (0.4)	44.0 (0.2)	43.8 (0.1)	0.04	0.25	0.01	0.15
D1 (Gy)	47.1 (0.5)	47.6 (0.5)	46.8 (0.5)	<0.01	<0.01	0.08	<0.01
Bowel							
V45 (%)	29.5 (16.4)	9.9 (4.8)	7.6 (5.6)	<0.01	<0.01	<0.01	0.4
V45 (cc)	367 (195)	105 (52)	76 (44)	<0.01	<0.01	<0.01	0.35
V40 (%)	48.5 (14.8)	21.4 (8.3)	17.4 (9.3)	<0.01	<0.01	<0.01	0.01
Rectum							
V45 (%)	75.0 (20.1)	32.4 (11.1)	24.3 (10.0)	<0.01	<0.01	<0.01	0.09
V40 (%)	97.0 (2.5)	73.6 (14.2)	63.9 (16.6)	<0.01	<0.01	<0.01	<0.01
Bladder							
V45 (%)	62.6 (29.6)	39.8 (9.2)	24.9 (13.1)	<0.01	<0.01	<0.01	0.01
V40 (%)	98.5 (6.2)	80.9 (13.8)	72.0 (17.5)	<0.01	<0.01	<0.01	<0.01
Left femoral head							
V45 (%)	12.5 (10.8)	0.0 (0.0)	0.0 (0.0)	<0.01	<0.01	<0.01	1
V30 (%)	49.9 (16.2)	11.5 (2.0)	8.4 (2.7)	<0.01	<0.01	<0.01	0.28
Right femoral head							
V45 (%)	11.2 (12.1)	0.0 (0.0)	0.0 (0.0)	<0.01	<0.01	<0.01	1
V30 (%)	49.0 (17.2)	11.6 (1.6)	7.3 (2.5)	<0.01	<0.01	<0.01	0.16
CIRTOG	1.61 (0.28)	1.01 (0.06)	0.83 (0.09)	<0.01	<0.01	<0.01	<0.01
CN	0.43 (0.06)	0.83 (0.03)	0.77 (0.07)	<0.01	<0.01	<0.01	<0.01
HI	0.07 (0.01)	0.08 (0.01)	0.07 (0.01)	<0.01	<0.01	0.76	<0.01

Total MU (MU)	200 (9)	1125 (100)	536 (97)	<0.01	<0.01	<0.01	<0.01
Estimated delivery time (mins)	1.39 (0.02)	6.89 (0.25)	2.63 (0.01)	<0.01	<0.01	<0.01	<0.01

Table 2: Comparison of dosimetric parameters for PTV1.5.

OAR doses

There was a difference between techniques for all OAR dosimetric parameters for all uterine margins (p 0.01) except right femoral head V45 for PTV3 (p=0.07). On further paired comparisons, dosimetric parameters for OAR were significantly higher with 4FRT compared with IMRT (p 0.05) or VMAT (p 0.05) (Tables 2-5). For PTV1.5, higher doses were seen with IMRT than VMAT on paired comparison for bowel V40, rectum V40, bladder V40 and V45 (p 0.01) but there were no differences in femoral doses between these advanced planning techniques (Table 2). For PTV2, higher doses were seen with IMRT than VMAT for bowel V40 (p=0.04) and rectum V40 (p=0.02), but there were no differences in bladder or femoral doses (Table 3). For the larger uterine margins (PTV2.5 and PTV3), there were no differences in OAR doses between IMRT and VMAT on paired comparison (Tables 4 and 5).

Conformity indices

There was a statistically significant difference between techniques for CIRTOG (p<0.01) and CN (p<0.01) for all uterine margins (Tables 2-5), with superior conformity seen in IMRT and VMAT plans compared with 4FRT on paired comparisons using both indices (p<0.01). Conformity was superior with IMRT than VMAT for both indices and for all uterine margins (p 0.03), with the exception of CT_{RTOG} for PTV3 where there was no significant difference between IMRT and VMAT.

Homogeneity index

Homogeneity index using HI was significantly different between techniques for all uterine margins (Tables 2-5) except PTV2.5 (p=0.27). For the uterine margins where there was a significant difference, paired comparison revealed that homogeneity was significantly inferior with IMRT compared with either 4FRT (p<0.01) or VMAT (p<0.01), with no difference between 4FRT and VMAT.

Variables	**4FRT**	**IMRT**	**VMAT**	**Overall technique comparison**	**4FRT *vs* IMRT**	**4FRT *vs* VMAT**	**IMRT *vs* VMAT**
	(n=20)	**(n=20)**	**(n=20)**	**p value**	**p value**	**p value**	**p value**
	mean (sd)	**mean (sd)**	**mean (sd)**				
PTV							
V45 (%)	83.2 (9.5)	90.5 (2.5)	79.3 (6.0)	<0.01	<0.01	0.07	<0.01
V42.75 (%)	99.8 (0.3)	99.1 (0.1)	99.6 (0.3)	<0.01	<0.01	0.01	<0.01
D99 (Gy)	43.5 (0.6)	42.8 (0.1)	43.3 (0.3)	<0.01	<0.01	0.08	<0.01
D97 (Gy)	44.1 (0.5)	43.9 (0.1)	43.9 (0.2)	0.21	0.25	0.08	0.54
D1 (Gy)	47.0 (0.4)	47.6 (0.6)	46.7 (0.5)	<0.01	<0.01	0.03	<0.01
Bowel							
V45 (%)	29.5 (16.4)	11.0 (6.0)	9.1 (6.1)	<0.01	<0.01	<0.01	0.5
V45 (cc)	367 (195)	101 (50)	88 (47)	<0.01	<0.01	<0.01	0.7
V40 (%)	48.5 (14.8)	22.6 (8.9)	19.3 (9.1)	<0.01	<0.01	<0.01	0.04
Rectum							
V45 (%)	75.0 (20.1)	33.8 (9.7)	24.7 (10.9)	<0.01	<0.01	<0.01	0.07
V40 (%)	97.0 (2.5)	75.6 (14.2)	67.8 (18.0)	<0.01	<0.01	<0.01	0.02
Bladder							
V45 (%)	62.6 (29.6)	34.6 (13.2)	29.1 (13.8)	<0.01	<0.01	<0.01	0.4

V40 (%)	98.5 (6.2)	80.0 (17.3)	77.5 (16.7)	<0.01	<0.01	<0.01	0.41
Left femoral head							
V45 (%)	12.5 (10.8)	0.1 (0.2)	0.0 (0.0)	<0.01	<0.01	<0.01	0.98
V30 (%)	49.9 (16.2)	11.3 (1.7)	8.3 (3.1)	<0.01	<0.01	<0.01	0.32
Right femoral head							
V45 (%)	11.2 (12.1)	0.0 (0.0)	0.0 (0.0)	<0.01	<0.01	<0.01	1
V30 (%)	49.0 (17.2)	11.0 (1.5)	8.2 (3.0)	<0.01	<0.01	<0.01	0.36
CIRTOG	1.55 (0.27)	0.98 (0.06)	0.83 (0.07)	<0.01	<0.01	<0.01	0.01
CN	0.43 (0.06)	0.83 (0.02)	0.76 (0.06)	<0.01	<0.01	<0.01	<0.01
HI	0.07 (0.01)	0.08 (0.01)	0.07 (0.01)	<0.01	<0.01	0.83	<0.01
Total MU (MU)	200 (9)	1125 (105)	527 (80)	<0.01	<0.01	<0.01	<0.01
Delivery time (mins)	1.39 (0.02)	6.89 (0.27)	2.63 (0.01)	<0.01	<0.01	<0.01	<0.01

Table 3: Comparison of dosimetric parameters for PTV2.

Total MU and estimated delivery time

Total MU and estimated delivery time were significantly different between techniques for all uterine margins ($p<0.01$) with higher values seen using IMRT (mean: 1125-1138 MU, 6.89-6.92 minutes for PTV1.5 to PTV3), followed by VMAT (mean: 490-536 MU, 2.63 minutes for PTV1.5 to PTV3) then 4FRT (mean: 200-202 MU, 1.39 minutes for PTV1.5 to PTV3) (Tables 2-5).

Comparison between uterine margins

The differences detected between techniques for the various parameters for each uterine margin were not significantly different between uterine margins (Table 6).

Planning and calculation times

Statistical analysis of planning times was not conducted, as times were not recorded for all patients. However, for the patients that were recorded, average (range) planning and calculation times are summarized. For 4FRT, average planning time was 15 minutes (range: 10-18 minutes) with average calculation time of 2 minutes (range: 1-3 minutes).

For IMRT, average planning time was 220 minutes (range: 150-255 minutes) and average calculation time was 10 minutes (range: 7-15 minutes). For VMAT, average planning time was 120 minutes (range: 90-160 minutes) and average calculation time was 45 minutes (range: 30-65 minutes).

Discussion

This study demonstrates that excellent target coverage can be achieved using 4FRT, IMRT or VMAT in the definitive management of cervical cancer. Although some statistically significant differences were seen in PTV coverage between techniques, these differences would not be clinically significant. In addition, IMRT and VMAT plans resulted in significantly lower doses to OAR compared with 4FRT, which is consistent with results from other dosimetry studies in cervical cancer that compared 4FRT with IMRT or VMAT [6-8]. This current study, however, also demonstrates that IMRT and VMAT significantly lower dose to OAR compared with 4FRT regardless of CTV to PTV margin size used to account for uterine motion. Multiple studies have compared IMRT and VMAT in cervical cancer [24]. Cozzi et al. [25] studied single arc VMAT versus 5 fields IMRT in 8 cervical cancer patients and found comparable target coverage with both techniques, but superior OAR sparing, homogeneity and conformity with VMAT.

Variables	**4FRT**	**IMRT**	**VMAT**	**Overall technique comparison**	**4FRT *vs* IMRT**	**4FRT *vs* VMAT**	**IMRT *vs* VMAT**
	(n=11)	**(n=11)**	**(n=11)**	**p value**	**p value**	**p value**	**p value**
	mean (sd)	**mean (sd)**	**mean (sd)**				
PTV							
V45 (%)	84.2 (8.5)	91.4 (2.3)	79.4 (7.5)	<0.01	0.02	0.11	<0.01
V42.75 (%)	99.8 (0.4)	99.0 (0.0)	99.5 (0.3)	<0.01	<0.01	0.02	<0.01
D99 (Gy)	43.4 (0.5)	42.8 (0.0)	43.2 (0.3)	<0.01	<0.01	0.07	<0.01
D97 (Gy)	44.1 (0.4)	44.0 (0.1)	43.8 (0.1)	0.14	0.45	0.05	0.2
D1 (Gy)	47.0 (0.5)	47.8 (0.2)	46.8 (0.5)	<0.01	<0.01	0.4	<0.01

Bowel							
V45 (%)	30.3 (18.7)	12.1 (6.9)	9.8 (7.9)	<0.01	<0.01	<0.01	0.49
V45 (cc)	338 (220)	127 (62)	100 (70)	<0.01	<0.01	<0.01	0.53
V40 (%)	46.4 (16.2)	21.7 (10.1)	19.1 (11.4)	<0.01	<0.01	<0.01	0.24
Rectum							
V45 (%)	73.3 (22.9)	32.0 (12.0)	30.9 (8.2)	<0.01	<0.01	<0.01	0.88
V40 (%)	96.5 (2.9)	75.3 (15.8)	67.1 (21.4)	<0.01	<0.01	<0.01	0.09
Bladder							
V45 (%)	67.6 (24.2)	35.7 (12.8)	26.4 (14.5)	<0.01	<0.01	<0.01	0.28
V40 (%)	97.5 (8.4)	84.2 (12.6)	78.2 (16.9)	<0.01	<0.01	<0.01	0.07
Left femoral head							
V45 (%)	15.2 (11.2)	0.0 (0.0)	0.0 (0.0)	<0.01	<0.01	<0.01	1
V30 (%)	55.0 (14.0)	11.3 (1.8)	9.4 (2.4)	<0.01	<0.01	<0.01	0.59
Right femoral head							
V45 (%)	12.4 (12.3)	0.0 (0.0)	0.0 (0.0)	<0.01	<0.01	<0.01	1
V30 (%)	50.5 (16.4)	10.8 (1.6)	8.7 (2.6)	<0.01	<0.01	<0.01	0.6
CIRTOG	1.53 (0.23)	1.0 (0.04)	0.83 (0.09)	<0.01	<0.01	<0.01	0.01
CN	0.43 (0.05)	0.85 (0.06)	0.75 (0.07)	<0.01	<0.01	<0.01	<0.01
HI	0.07 (0.01)	0.09 (0.00)	0.08 (0.05)	0.27	0.12	0.26	0.64
Total MU (MU)	202 (8)	1138 (100)	536 (65)	<0.01	<0.01	<0.01	<0.01
Delivery time (min)	1.39 (0.02)	6.92 (0.26)	2.63 (0.01)	<0.01	<0.01	<0.01	<0.01

Table 4: Comparison of dosimetric parameters for PTV2.5.

Variables	**4FRT**	**IMRT**	**VMAT**	**Overall technique comparison**	**4FRT *vs* IMRT**	**4FRT *vs* VMAT**	**IMRT *vs* VMAT**
	(n=7)	**(n=7)**	**(n=7)**	**p value**	**p value**	**p value**	**p value**
	mean (sd)	**mean (sd)**	**mean (sd)**				
PTV							
V45 (%)	82.4 (10.7)	88.8 (4.8)	80.2 (3.9)	0.11	0.12	0.59	0.05
V42.75 (%)	99.7 (0.5)	99.0 (0.1)	99.4 (0.3)	<0.01	<0.01	0.09	0.04
D99 (Gy)	43.1 (0.7)	42.8 (0.0)	43.1 (0.3)	0.36	0.2	0.89	0.24
D97 (Gy)	44.0 (0.5)	43.9 (0.2)	43.8 (0.2)	0.6	0.84	0.35	0.46
D1 (Gy)	46.9 (0.6)	47.7 (0.3)	47.0 (0.4)	<0.01	<0.01	0.84	<0.01
Bowel							
V45 (%)	34.0 (18.1)	13.4 (8.9)	9.2 (4.4)	<0.01	<0.01	<0.01	0.44
V45 (cc)	388 (240)	131 (69)	102 (54)	<0.01	<0.01	<0.01	0.65
V40 (%)	49.8 (12.5)	23.4 (6.9)	20.4 (8.3)	<0.01	<0.01	<0.01	0.21

Rectum							
V45 (%)	67.3 (26.9)	35.4 (9.5)	28.8 (9.1)	<0.01	0.01	<0.01	0.52
V40 (%)	95.8 (3.4)	76.2 (14.1)	70.8 (17.3)	<0.01	<0.01	<0.01	0.27
Bladder							
V45 (%)	61.7 (25.9)	29.9 (12.1)	22.3 (19.6)	0.01	0.01	<0.01	0.51
V40 (%)	100.0 (0.0)	90.9 (6.7)	85.4 (12.3)	<0.01	0.02	<0.01	0.13
Left femoral head							
V45 (%)	14.0 (12.8)	0.0 (0.0)	0.0 (0.0)	0.01	<0.01	<0.01	1
V30 (%)	56.1 (15.5)	12.5 (2.1)	9.7 (2.1)	<0.01	<0.01	<0.01	0.55
Right femoral head							
V45 (%)	7.6 (11.0)	0.0 (0.0)	0.0 (0.0)	0.07	0.05	0.05	1
V30 (%)	45.3 (17.6)	11.6 (1.6)	9.8 (1.5)	<0.01	<0.01	<0.01	0.75
CIRTOG	1.43 (0.27)	0.95 (0.07)	0.83 (0.05)	<0.01	<0.01	<0.01	0.19
CN	0.41 (0.05)	0.83 (0.05)	0.77 (0.03)	<0.01	<0.01	<0.01	0.03
HI	0.07 (0.01)	0.09 (0.01)	0.07 (0.01)	<0.01	<0.01	0.46	<0.01
Total MU (MU)	202 (10)	1132 (96)	490 (38)	<0.01	<0.01	<0.01	<0.01
Delivery time (mins)	1.39 (0.02)	6.91 (0.24)	2.63 (0.01)	<0.01	<0.01	<0.01	<0.01

Table 5: Comparison of dosimetric parameters for PTV3.

In another study, Sharfo et al. [26] compared 5 different planning techniques in 10 patients and found 12 and 20 field IMRT resulted in better plan quality than single and dual arc VMAT. Guy et al. [7] reported reduced small bowel mean dose and a trend towards reduced rectal dose with VMAT whilst a meta-analysis of eight studies by Bai et al. [24] suggested lower rectum V40 with VMAT compared with IMRT but no differences in bladder or bowel dose. Differences in these studies are likely related to variations in contouring definitions and planning strategies including the number of fields or arcs and optimization algorithms [4,24].

Dual arc VMAT and 9 fields IMRT were used for the current study as they are used routinely within the department for other tumor sites. These two techniques were comparable in target coverage, however, VMAT plans displayed superior homogeneity and better rectal and bowel sparing for smaller uterine margins but inferior conformity compared with IMRT. VMAT plans were also delivered more efficiently, with shorter treatment times and lower MU compared with IMRT, which is consistent with other studies [24]. It is expected that the superior OAR sparing achieved with these advanced planning techniques will translate to a reduction in toxicities in clinical practice and there is early data to support this. A meta-analysis by Lin et al. [10] of six prospective and retrospective studies comparing IMRT and 4FRT in cervical cancer demonstrated significantly less acute grade 2-4 gastrointestinal and genitourinary toxicities and chronic grade 3 genitourinary toxicities with IMRT compared with 4FRT with similar disease-free survival and overall survival. Intrafraction and interfraction uterine motion may result in a geographical miss with IMRT or VMAT and therefore, adequate PTV margins are required to account for uterine motion in a patient [15]. Position changes of up to 4 cm have been suggested, thereby necessitating generous PTV margins for the uterus to ensure target coverage [13]. There may be little benefit in using IMRT or VMAT compared with 4FRT when large margins are needed to accommodate uterine motion as OAR will also be included within the PTV unnecessarily. Therefore, Ahmad et al. [14] suggested using 4FRT for margins beyond 2.5 cm to save planning and delivery time [14]. The current study, however, demonstrated that even with large PTV margins up to 3 cm, advanced planning techniques resulted in superior OAR sparing compared with 4FRT. Uterine motion is complex and patient-specific and therefore, the use of population-based margins is not ideal [15].

Variables	F (numerator DF, denominator DF)	p value
PTV		
V45 (%)	0.25 (6,70)	0.96
V42.75 (%)	0.26 (6,70)	0.95
D99 (Gy)	0.65 (6,70)	0.69
D97 (Gy)	0.16 (6,70)	0.99
D1 (Gy)	0.66 (6,70)	0.68
Bowel		
V45 (%)	0.16 (6,70)	0.99

V45 (cc)	0.35 (6,70)	0.91
V40 (%)	0.48 (6,70)	0.82
Rectum		
V45 (%)	0.65 (6,70)	0.69
V40 (%)	0.44 (6,70)	0.85
Bladder		
V45 (%)	0.38 (6,70)	0.89
V40 (%)	1.65 (6,70)	0.15
Left femoral head		
V45 (%)	0.26 (6,70)	0.95
V30 (%)	0.53 (6,70)	0.78
Right femoral head		
V45 (%)	0.32 (6,70)	0.92
V30 (%)	0.33 (6,70)	0.92
CIRTOG	0.74 (6,70)	0.62
CN	0.66 (6,70)	0.68
HI	0.70 (6,70)	0.65
Total MU (MU)	0.48 (6,70)	0.82
Estimated delivery time (mins)	0.06 (6,70)	1

Table 6: F-tests assessing for differential technique effects over the different uterine margins.

Various strategies have been suggested to accommodate uterine motion such as anisotropic margins, planning CT scans with full and empty bladder, and adaptive strategies using IGRT [13]. Online adaptive strategies such as plan of the day [14] are promising and can result in excellent OAR sparing without compromising target coverage, however, are resource-intense and may be difficult to implement in a busy department. Whichever strategy is employed, appropriate image guidance is imperative when using IMRT or VMAT for intact cervical cancer, preferably with daily online imaging given the complex nature of uterine movement [15]. IMRT and VMAT are resource-intensive techniques and their dosimetric advantages come at the expense of increased planning and delivery requirements. Compared with 4FRT, planning and treatment times are longer and technological requirements are greater, impacting on the costs and efficiency of a department [27]. With daily image guidance, VMAT and IMRT are both acceptable techniques for definitive radiotherapy in locally advanced cervical cancer. The faster treatment delivery time with VMAT is advantageous in cervical cancer where intrafraction uterine motion may be a concern. Ultimately, the choice between the use of IMRT and VMAT may be patient and department specific. There are several limitations to this study. It is a dosimetric study and retrospective in nature. Isotropic margins were used for simplicity, rather than anisotropic margins described in organ motion studies. Also, planning CT scans were not carried out with full and empty bladder protocols to account for uterine motion to some extent. Finally, patient numbers were small, particularly in the comparison of techniques with the larger uterine PTV margins.

Conclusion

Excellent target coverage was achieved with 4FRT, IMRT and VMAT, however, there was better OAR sparing with IMRT and VMAT compared with 4FRT regardless of CTV to PTV margin used to account for uterine motion. Compared with IMRT, VMAT plans had slightly better sparing of bowel and rectum (V40) for smaller uterine margins and greater homogeneity for most margins, however, IMRT plans displayed superior conformity. VMAT plans were associated with lower MU and faster delivery times compared with IMRT. This treatment efficiency is advantageous in cervical cancer radiotherapy where uterine motion during treatment delivery may result in geographic miss or target under coverage if inadequate uterine margins are used. Given the interfraction and intrafraction variation in uterine position, accurate localization of the uterus with daily image guidance is essential when considering IMRT or VMAT in cervical cancer. Longer term clinical outcome data showing reduced toxicity rates whilst maintaining tumor control is required to further support the use of these advanced planning techniques as standard.

Acknowledgment

The authors would like to acknowledge Sarah Gallagher, Joseph Hanna, and the radiation oncology staff at Calvary Mater Newcastle for their assistance with this project. No funding was received.

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