

Original Article



Cervical cancer patient reported gastrointestinal outcomes: intensity/volumetric modulated vs. 3D conformal radiation therapy

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ABSTRACT

Objective: To evaluate gastrointestinal (GI) patient reported outcomes (PROs) in cervical cancer patients treated with definitive radiotherapy (RT), comparing 3D conformal RT (3DCRT) vs. intensity modulated/volumetric modulated arc therapy (IMRT/VMAT).
Methods: An analysis of patients treated with definitive RT between 2015–2018 was performed. GI PROs were prospectively collected at baseline, during RT (acute), ≤12 weeks after RT (subacute), and >12 weeks after RT (late). GI PROs evaluated three symptom domains: bowel problems (BPs), bowel bother (BB), and abdominal problems (APs). Multiple linear regression analysis was performed to investigate associations between mean changes of symptom scores with clinical and dosimetric variables.
Results: The cohort included 167 patients. A total of 100 (60%) patients were treated with IMRT/VMAT and 67 (40%) with 3DCRT. In the subacute phase, the mean change of symptom scores from baseline in 3DCRT vs. IMRT/VMAT were +0.9 vs. -1.15 (p=0.004) for BP, +2.18 vs. -0.10 (p=0.019) for BB, and +1.41 vs. -0.38 (p=0.021) for AP. Likewise, in the late phase, mean changes were +0.72 vs. -0.82 (p=0.014) for BP, +1.98 vs. -0.03 (p=0.008) for BB, and +1.29 vs. -0.31 (p<0.001) for AP. On multiple linear regression, use of 3DCRT vs. IMRT/VMAT was associated with greater mean changes in subacute BP (p=0.023) and late phase AP (p=0.019). A higher small bowel V50Gy was associated increased symptom scores in late AP (p=0.012).
Conclusion: 3DCRT was associated with significantly greater worsening of GI PRO symptom scores in the subacute and late phase. These data support the ongoing use of IMRT/VMAT in routine practice.

Keywords: Cervical Cancer; Patient Reported Outcome Measures; Gastrointestinal Tract; Abnormalities, Radiation Induced; Radiotherapy, Conformal; Radiotherapy, Intensity-Modulated

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Data Sharing Statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Author Contributions

Conceptualization: U.R., L.P., Z.S., S.I., O.R., B.F., H.C., T.A., H.S.N.; Data curation: U.R., Z.S., S.I., H.S.N.; Formal analysis: U.R., Z.S., S.I., G.L., H.S.N.; Funding acquisition: U.R., H.S.N.; Investigation: U.R., W.J., G.L., H.S.N.; Methodology: U.R., W.J., O.R., B.F., T.A., G.L., H.S.N.; Project administration: U.R., H.S.N.; Software: G.L.; Supervision: L.P., O.R., H.C., T.A., H.S.N.; Validation: U.R., G.L., H.S.N.; Visualization: H.S.N.; Writing - original draft: U.R.; Writing - review & editing: W.J., L.P., Z.S., S.I., O.R., B.F., H.C., T.A., H.S.N.

Synopsis

This retrospective review revealed that cervical cancer patients treated with 3DCRT had more significant subacute and late gastrointestinal patient reported toxicity compared to those treated with IMRT/VMAT. Outcomes were similar regardless of radiotherapy technique. Our data supports the ongoing use of IMRT/VMAT in routine practice.

INTRODUCTION

Cervical cancer is the fourth most common type of cancer and is the fourth leading cause of cancer mortality in women worldwide [1]. Radical radiotherapy (RT) plays a significant role in the definitive management of locally advanced disease with survival rates at eight years of up to 67% when combined with concurrent chemotherapy [2]. External beam RT (EBRT) delivered with a brachytherapy (BT) boost is standard of care [3], and it has been shown to improve survival outcomes relative to EBRT alone in a large database analysis [4].

Treatment volumes for definitive RT for locally advanced cervix cancer include regional pelvic plus para-aortic lymph nodes depending on patients' risk stratification based on guidelines proposed by the ongoing EMBRACE II study [5]. As a result, adjacent gastrointestinal (GI) organs at risk (OARs), such as the rectum, sigmoid colon, and small bowel are within the irradiated volume. Irradiation of these structures contributes to GI morbidity during and after definitive RT [6]. This morbidity can be captured more reliably with patient reported outcomes (PROs) compared to physician-scored toxicity, which has been shown to underestimate the patient's toxicity experience [7].

The technique used for definitive EBRT has evolved in the last decade. Traditionally, conventional 3D conformal EBRT (3DCRT) technique, which utilized 3–4 fields with fixed apertures conforming to a contoured planning target volume (PTV) were used [8]. In contrast, modern EBRT techniques such as intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) incorporate 7–9 beam angles (IMRT) or continuous gantry motion (VMAT) along with computerized optimization of dynamic beam apertures. These modern techniques allow more conformal radiation delivery to the PTV while reducing the dose to surrounding normal tissues [9]. The ability of IMRT and VMAT to spare GI structures may reduce the risk of GI toxicity during treatment [10], as shown in the post-operative endometrial and cervical cancer setting [11].

However, there is a lack of data regarding the impact of IMRT/VMAT techniques on patient reported GI outcomes in the definitive RT setting for cervix cancer. The purpose of this study was to retrospectively analyze GI PROs in patients who completed Prospective Outcomes and Support Initiative (POSI) gynecologic cancer specific questionnaires during and after RT for locally advanced cervical cancer [12,13]. We hypothesized that PROs would reveal less acute and late toxicity in the IMRT/VMAT group of patients compared to those treated with 3DCRT techniques.

MATERIALS AND METHODS

1. Patient population

All patients with biopsy confirmed cervix carcinoma who were treated at our provincial institution with definitive radical EBRT and BT boost with or without chemotherapy between 2015–2018 were retrospectively analyzed. At our institution, it is standard that cervical cancer patients treated with definitive radiotherapy are staged with positron emission tomography (PET) scans. Patients treated with palliative or adjuvant RT and those without a baseline POSI score were excluded. This study received ethics approval through our institution and the University of British Columbia Human Ethics Department.

Our institution is comprised of six regional cancer centres and serves a population of 5.5 million. During the study period, the use of IMRT/VMAT varied between regional cancer centres based on physician preference. EBRT was delivered according to institutional protocol and comprised of either conventional 3DCRT techniques or IMRT/VMAT techniques with daily image guidance. 3DCRT techniques generally consisted of a “four field box” beam arrangement using anterior-posterior and lateral parallel opposed pair fields to cover the PTV with prescription dose of 45Gy in 25 fractions. IMRT/VMAT techniques were based on contours from the EMBRACE II protocol depending on patient risk stratification [5]. Gross tumor volumes (GTV) were contoured for primary disease and involved lymph nodes on planning computed tomography (CT) simulation, PET/CT, and magnetic resonance imaging (MRI) scan. A high-risk clinical target volume (CTV) included the GTV and whole cervix. A low-risk CTV included the high-risk CTV and a 2–3 cm margin along the vaginal axis, whole uterine corpus, and complete bilateral parametria. An internal target volume was created to account for uncertainties in size, shape, and position of the low-risk CTV. An elective CTV volume treated at risk regional lymph nodes including the presacral, common iliac, pelvic, and inguinal (if distal 1/3rd vaginal involvement) nodes. Para-aortic lymph nodes were included in patients with positive pelvic or para-aortic nodes. Finally, a PTV margin was added to account for random and systematic setup errors. 45Gy in 25 fractions was prescribed to the PTV. An EBRT boost of 55Gy and 57.5Gy was delivered to gross lymph nodes inside and outside the true pelvis, respectively. This boost was delivered via a simultaneous integrated boost in IMRT/VMAT treatments and as a sequential boost in 3DCRT treatments.

Patients with creatinine clearance >45 mL/min, adequate blood counts, no pre-existing hearing loss or neuropathy were considered for concurrent chemotherapy generally involving 5 weekly cisplatin (40 mg/m²).

The high-dose rate BT boost was delivered to a dose of 28–30Gy over 4–5 fractions using intracavitary applicators with or without interstitial needles. Per GEC-ESTRO guidelines, MRI guidance was used in all patients, with a total equivalent dose in 2Gy fractions to 90–95Gy [14].

GI OARs were contoured as per institutional protocol for external beam planning. The small bowel was contoured as a potential space for small bowel as per the CT simulation scan, the sigmoid was contoured from the rectosigmoid junction to the left iliac fossa, and the rectum was contoured from the rectosigmoid junction superiorly to the anal canal inferiorly. These structures were also contoured for each brachytherapy fraction.

2. Patient reported outcomes analysis

All patients recorded their GI symptomatology via the POSI questionnaire. POSI is a provincial platform used for symptom assessment in a variety of tumor groups at our institution [12]. In this electronic survey, there are three GI domains including bowel problems (BPs), bowel bother (BB), and abdominal problems (APs) which are based on validated questionnaires from the Expanded Prostate Cancer Index Composite (EPIC) Bowel 2, Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE), and European Organisation for Research and Treatment for Cancer Quality-of-Life Questionnaire Cervical Cancer Module (EORTC QLQ CX24) [15-17]. Each domain has a series of individual questions with scores generally ranging from 0–4. Higher scores indicate more patient toxicity. The specific questions are highlighted in **Fig. S1**. The sum BP score ranges from 0–26, the sum BB score ranges from 0–28, and the sum AP score ranges from 0–24. This questionnaire is administered to patients via an iPad during clinical visits at the time of consultation for a baseline assessment, during RT at weekly patient review appointments, at six weeks post-RT, and during all subsequent follow-up clinical appointments with their radiation oncologist. We evaluated the mean change in sum score and mean change in individual question maximum score of each GI domain during RT (acute), ≤ 12 weeks after completion of RT (subacute), and > 12 weeks (late) after RT compared to baseline POSI scores.

3. Statistical analysis

The cohort's clinicopathologic variables were analyzed including sex, smoking status, histology, previous abdominal surgery, previous GI medical conditions, International Federation of Gynecology and Obstetrics (FIGO) 2014 edition stage, and pelvic or para-aortic lymph node involvement. RT variables were analyzed including EBRT technique (3DCRT vs. IMRT/VMAT), EBRT volume (pelvis +/- para-aortic fields), dose, fractionation, use of EBRT boost, BT dose and fractionation, duration of therapy, and use of concurrent chemotherapy. Dosimetric variables included Dmax (maximum dose), V (volume) parameters of EBRT, and D2cc (highest dose to 2 cc) of brachytherapy plans for the small bowel, sigmoid, and rectum. Associations between groups or categorical variables were tested using the χ^2 test, Fisher's Exact test, or Mann-Whitney U test where appropriate. Associations between continuous and categorical variables were tested using a t-test.

The Kaplan Meier method was used to estimate survival. Overall survival (OS) was defined as date of diagnosis to date of death from any cause. Local control (LC) was defined as no evidence of relapse in the primary site and regional control (RC) was defined as no evidence of relapse in the regional lymph nodes. Patients were censored at the date of last follow-up or death. Survival outcomes were stratified based on EBRT technique. The log-rank test was used to compare the survival distributions between groups. Multiple linear regression models were used to investigate the association between the mean change in POSI scores in each symptom domain at each time phase (acute, subacute, late) and age, smoking status, previous abdominal surgery, previous GI medical conditions, FIGO 2014 stage, EBRT technique (3DCRT vs. IMRT/VMAT), EBRT volume (pelvis vs. para-aortic), use of EBRT boost, concurrent chemotherapy, and dosimetric variables. To deal with a high degree of correlation between multiple dosimetry variables, we selected the dosimetry variables to be included in the final models using stepwise regression with cross validation. The selected dosimetry variables were then used in a multivariable linear regression model along with other clinically relevant variables to model the change in mean symptom scores. Statistical analysis was performed using SAS Version 9.4 for Microsoft Windows (SAS Institute Inc., Cary, NC, USA). An alpha level of 0.05 was used for all statistical tests.

RESULTS

1. Cohort

Between 2015 and 2018, 296 cervical carcinoma patients were treated at our institution with RT. After exclusions (n=37 patients who were treated with adjuvant RT, n=11 patients treated without BT boost, and n= 81 without baseline POSI scores) 167 patients were eligible for analysis. Patient demographics, GI comorbidities, smoking status, FIGO 2014 edition stage, and tumor characteristics are summarized in **Table 1** stratified by EBRT technique.

A total of 100 patients (60%) were treated with IMRT/VMAT and 67 patients (40%) were treated with 3DCRT. Typical dose colour wash distributions for 3DCRT and VMAT in the axial, coronal, and sagittal planes are outlined in **Fig. S2**. 50% of patients in the IMRT/VMAT cohort had pelvic or para-aortic lymph node involvement compared to 30% of the 3DCRT cohort (p=0.016).

Treatment characteristics are outlined in **Table 2**. 98% of patients received concurrent chemotherapy. Chemotherapy was omitted for n=2 with lower risk disease (stage IA2), n=1 with stage IIA1 who declined concurrent chemotherapy, and n=1 for cardiac comorbidities. 38% of patients in the IMRT/VMAT cohort were treated with para-aortic irradiation compared to 19% in the 3DCRT cohort (p=0.011).

Table 1. Patient and tumor characteristics

Characteristics	3DCRT (n=67)	IMRT/VMAT (n=100)	p-value
Demographics			
Median age at diagnosis (range)	52 years (range: 27–86)	47 years (range: 27–86)	0.197
Previous abdominal/pelvic surgery	None: 53 (79.1%) Bowel surgery: 1 (1.5%) Non-bowel surgery: 13 (19.4%)	None: 89 (89.0%) Bowel surgery: 1 (1.0%) Non-Bowel surgery: 10 (10.0%)	0.211
Previous GI medical conditions	None: 66 (98.5%) Irritable bowel syndrome: 0 Inflammatory bowel disease: 0 Celiac: 0 Prior diverticulitis: 0 Primary biliary cholangitis: 1 (1.5%)	None: 96 (96.0%) Irritable bowel syndrome: 1 (1.0%) Inflammatory bowel disease: 1 (1.0%) Celiac: 1 (1.0%) Prior diverticulitis: 1 (1.0%) Primary biliary cholangitis: 0	0.521
Smoking status			0.283
Lifelong non-smokers	42 (62.7%)	57 (57.0%)	
Ex-smoker	17 (25.4%)	22 (22.0%)	
Current smokers	7 (10.4%)	21 (21.0%)	
Unknown	1 (1.5%)	0	
Disease factors			
FIGO 2014 stage			0.016
IA1	0	1 (1.0%)	
IA2	0	2 (2.0%)	
IB1	10 (14.9%)	10 (10.0%)	
IB2	8 (11.9%)	6 (6.0%)	
IIA1	7 (10.4%)	4 (4.0%)	
IIB	18 (26.9%)	20 (20.0%)	
IIIA	0	2 (2.0%)	
IIIB	4 (6.0%)	5 (5.0%)	
Pelvic lymph node involvement (new FIGO IIIC1)	19 (28.4%)	30 (30.0%)	
Para-aortic lymph node metastases (new FIGO IIIC2)	1 (1.5%)	20 (20.0%)	
Histology			
Squamous cell carcinoma	48 (71.6%)	76 (76.0%)	0.266
Adenocarcinoma	18 (26.9%)	18 (18.0%)	
Adenosquamous	1 (1.5%)	3 (3.0%)	
Small cell	0	4 (4.0%)	

3DCRT, 3D conformal radiotherapy; IMRT/VMAT, intensity modulated/volumetric modulated arc therapy; FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Treatment characteristics

Characteristics	3DCRT (n=67)	IMRT/VMAT (n=100)	p-value
External beam radiotherapy			
EBRT technique	3D conformal: 67 (100%)	IMRT: 5 (5.0%) VMAT: 95 (95.0%)	N/A
EBRT volume	Pelvis only: 54 (80.6%) Pelvis and para-aortics: 13 (19.4%)	Pelvis only: 62 (62.0%) Pelvis and para-aortics: 38 (38.0%)	0.011
Upper border of EBRT field for para-aortic fields	Superior L4: 1 (1.5%) Superior L3: 9 (13.4%) Superior L2: 3 (4.5%) Superior L1: 0 Superior T12: 0	Superior L4: 7 (7.0%) Superior L3: 6 (6.0%) Superior L2: 12 (12.0%) Superior L1: 10 (10.0%) Superior T12: 3 (3.0%)	0.005
Pelvis dose	40–44Gy: 0 45Gy: 66 (98.5%) 46–48Gy: 1 (1.5%)	40–44Gy: 1 (1.0%) 45Gy: 99 (99.0%) 46–48Gy: 0	0.339
Use of EBRT nodal boost	n=19 (28.4%) Median dose (range): 55.8Gy (50.4–61Gy)	n=48 (48.0%) Median dose (range): 55.0Gy (50–57.6Gy)	0.014
Brachytherapy			
BT boost dose	Median (range): 28Gy (6.5–30Gy)	Median (range): 28Gy (7–30Gy)	0.177
BT boost fractions	Median (range): 4 (1–5)	Median (range): 4 (1–5)	0.136
Chemotherapy			0.647
None	2 (3.0%)	2 (2.0%)	
Concurrent cisplatin	64 (95.5%)	94 (94.0%)	
Concurrent other	1 (1.5%)	4 (4.0%)	

3DCRT, 3D conformal radiotherapy; BT, brachytherapy; IMRT/VMAT, intensity modulated/volumetric modulated arc therapy.

2. Patient reported outcomes

All patients had baseline POSI scores in both cohorts. In the 3DCRT cohort, POSI assessments were completed by 63% of patients during RT, 73% \leq 12 weeks after RT, and 84% $>$ 12 weeks after RT. In the IMRT/VMAT cohort, POSI assessments were completed by 76% of patients during RT ($p=0.072$), 84% \leq 12 weeks after RT ($p=0.134$), and 87% $>$ 12 weeks after RT ($p=0.536$).

Baseline mean sum and maximum individual question BP scores were 2.57 (95% CI=1.89–3.26) and 2 in the 3DCRT cohort compared to 3.83 (95% CI=3.09–4.56) and 3 in the IMRT/VMAT cohort ($p=0.022$). Baseline mean sum and maximum individual question BB scores were 2.61 (95% CI=1.80–3.42) and 2 in the 3DCRT cohort compared to 3.29 (95% CI=2.48–4.09) and 3 in the IMRT/VMAT cohort ($p=0.264$). Baseline mean sum and maximum individual question AP scores were 1.83 (95% CI=1.20–2.46) and 2 in the 3DCRT cohort compared to 2.67 (95% CI=2.14–3.20) and 2 in the IMRT/VMAT cohort ($p=0.051$).

The mean change in sum POSI scores and mean change in individual maximum POSI question score of each GI domain (BP, BB, AP) during RT, \leq 12 weeks after completion of RT, and $>$ 12 weeks after RT compared to baseline scores is shown in **Fig. 1**. In the acute phase, there were no significant changes in mean sum or maximum individual symptom scores in all domains comparing 3DCRT and IMRT/VMAT. In the subacute and late phases, patients treated with 3DCRT experienced significantly greater mean sum and maximum symptom scores in all domains compared to IMRT/VMAT.

3. Dosimetric analysis

Mean dose volume parameters stratified by EBRT technique can be found in **Table S1**. Treatment with 3DCRT was associated with increased small bowel V40–45Gy ($p<0.05$), rectum V40–45Gy ($p<0.05$), and sigmoid V40–45Gy ($p<0.05$). Patients treated with IMRT/VMAT had an increased small bowel Dmax (maximum dose) ($p=0.013$), small bowel V15Gy ($p=0.007$), and brachytherapy rectum D2cc ($p=0.018$).

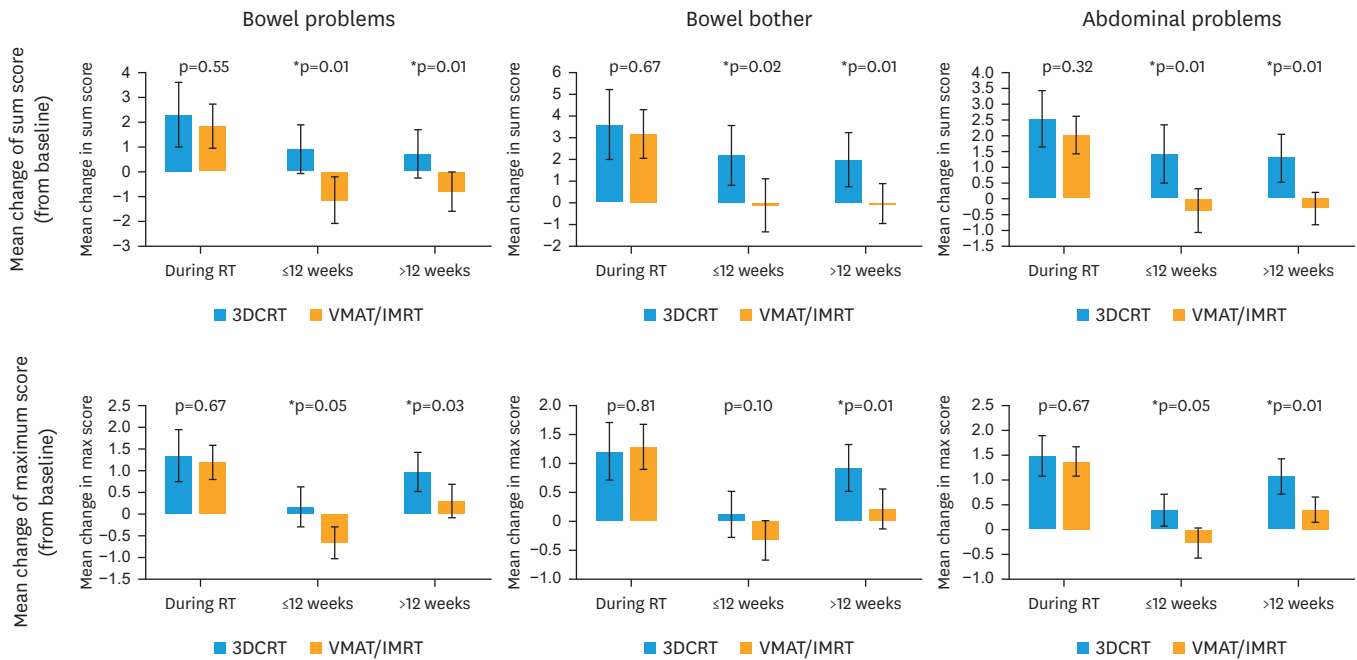


Fig. 1. Changes in Prospective Outcomes and Support Initiative symptom scores for each GI domain compared to baseline: during RT, ≤12 weeks after RT, and >12 weeks after RT. Error bars represent 95% confidence intervals.

3DCRT, 3D conformal radiotherapy; IMRT/VMAT, intensity modulated/volumetric modulated arc therapy; RT, radiotherapy.

*Statistically significant result.

4. Multiple linear regression analysis

The multiple linear regression analyses at each time phase are outlined in **Table 3**. In the acute phase, an EBRT treatment volume of the pelvis only vs. para-aortic was associated with reduced symptom scores in all domains ($p < 0.05$ for all). In the subacute phase, treatment with 3DCRT vs. IMRT/VMAT was associated with increased symptom scores in BP ($p = 0.023$). In the late phase, treatment with 3DCRT ($p = 0.019$) and higher small bowel V50Gy ($p = 0.012$) were associated increased symptom scores in AP. The sigmoid brachytherapy D2cc was associated with reduced symptom scores in subacute AP ($p = 0.027$) and late AP ($p = 0.018$). Age, smoking status, prior abdominal surgery, FIGO stage, use of EBRT boost, small bowel Dmax, small bowel D2cc, rectum Dmax, rectum V parameters, rectum D2cc, and sigmoid V parameters were not associated with symptom score changes in all domains ($p > 0.05$).

5. Survival outcomes

The median follow-up was 24 (range: 5–67) months. Three-year estimates of OS, LC, and RC 87%, 97%, 86% in the IMRT/VMAT cohort and 91% ($p = 0.323$), 97% ($p = 0.992$), and 92% ($p = 0.264$) in the 3DCRT cohort, respectively.

DISCUSSION

This contemporary population based retrospective cohort study revealed that patients treated with definitive EBRT with BT boost for cervical carcinoma have less patient reported subacute and late GI toxicity when treated with IMRT/VMAT compared to 3DCRT techniques. After incorporating dosimetric data with stepwise regression models, 3DCRT compared to IMRT/VMAT still predicted for increased symptom scores in the subacute BP and late AP domains.

Table 3. Multiple linear regression models of symptom scores at each time phase

Parameters	Bowel problems			Bowel bother			Abdominal problems				
	Estimate	p-value	95% CI	Estimate	p-value	95% CI	Estimate	p-value	95% CI		
Acute											
Pelvis vs. pelvis + para-aortic RT	-0.26	0.017	-0.47, -0.05	Pelvis vs. pelvis + para-aortic RT	-0.44	<0.001	-0.70, -0.18	Pelvis vs. pelvis + para-aortic RT	-0.24	0.008	-0.41, -0.06
3DCRT vs. IMRT	0.02	0.777	-0.15, 0.20	3DCRT vs. IMRT	-0.01	0.924	-0.22, 0.20	3DCRT vs. IMRT	-0.04	0.603	-0.19, 0.11
Age at diagnosis	0.00	0.570	0.00, 0.01	Age at diagnosis	0.01	0.107	0.00, 0.02	Age at diagnosis	0.00	0.324	0.00, 0.01
Non-smoker vs. current smoker	0.02	0.849	-0.21, 0.25	Non-smoker vs. current smoker	0.11	0.444	-0.17, 0.38	Non-smoker vs. current smoker	0.09	0.341	-0.10, 0.27
Ex smoker vs. current smoker	-0.05	0.684	-0.31, 0.20	Ex smoker vs. current smoker	0.01	0.933	-0.30, 0.32	Ex smoker vs. current smoker	0.02	0.823	-0.19, 0.23
No EBRT nodal boost vs. EBRT boost	-0.01	0.954	-0.29, 0.28	No EBRT nodal boost vs. EBRT boost	0.10	0.570	-0.24, 0.44	No EBRT nodal boost vs. EBRT boost	0.02	0.884	-0.21, 0.25
No prior abdominal surgery vs. prior abdominal surgery	0.17	0.153	-0.06, 0.41	No prior abdominal surgery vs. prior abdominal surgery	0.16	0.295	-0.14, 0.45	No prior abdominal surgery vs. prior abdominal surgery	0.01	0.890	-0.18, 0.21
FIGO Stage 3/4 vs. Stage 1/2	-0.02	0.295	-0.06, 0.02	FIGO stage 3/4 vs. stage 1/2	-0.01	0.741	-0.06, 0.04	FIGO Stage 3/4 vs. Stage 1/2	-0.01	0.738	-0.04, 0.03
Sigmoid D2cc	-0.01	0.099	-0.02, 0.00	Sigmoid D2cc	-0.01	0.253	-0.03, 0.01	Sigmoid D2cc	0.00	0.433	-0.02, 0.01
				Rectum V60Gy	0.09	0.010	0.02, 0.15	Small bowel V40Gy	0.00	0.159	0.00, 0.00
				Rectum D2cc	-0.02	0.051	-0.03, 0.00	Rectum D2cc	-0.01	0.102	-0.02, 0.00
Subacute											
3DCRT vs. IMRT	0.21	0.024	0.03, 0.39	3DCRT vs. IMRT	0.11	0.418	-0.16, 0.38	Sigmoid D2cc	-0.01	0.027	-0.03, 0.00
Age at diagnosis	0.00	0.440	0.00, 0.01	Age at diagnosis	0.00	0.639	-0.01, 0.01	3DCRT vs. IMRT	0.16	0.075	-0.02, 0.33
Non-smoker vs. current smoker	-0.11	0.357	-0.34, 0.12	Non-smoker vs. current smoker	0.02	0.886	-0.29, 0.34	Age at diagnosis	0.00	0.739	-0.01, 0.01
Ex smoker vs. current smoker	-0.12	0.364	-0.38, 0.14	Ex smoker vs. current smoker	-0.03	0.851	-0.39, 0.32	Non-smoker vs. current smoker	0.02	0.892	-0.20, 0.23
No EBRT nodal boost vs. EBRT boost	0.05	0.722	-0.24, 0.34	No EBRT nodal boost vs. EBRT boost	0.11	0.600	-0.31, 0.54	Ex smoker vs. current smoker	0.02	0.843	-0.22, 0.27
No prior abdominal surgery vs. prior abdominal surgery	0.16	0.177	-0.08, 0.40	No prior abdominal surgery vs. prior abdominal surgery	0.12	0.486	-0.21, 0.45	No EBRT nodal boost vs. EBRT boost	0.12	0.404	-0.16, 0.39
FIGO stage 3/4 vs. stage 1/2	0.00	0.977	-0.04, 0.04	FIGO stage 3/4 vs. stage 1/2	0.00	0.981	-0.06, 0.05	No prior abdominal surgery vs. prior abdominal surgery	0.03	0.766	-0.20, 0.27
Pelvis vs. pelvis + para-aortic RT	0.07	0.514	-0.14, 0.29	Pelvis vs. pelvis + para-aortic RT	0.02	0.878	-0.27, 0.31	FIGO stage 3/4 vs. stage 1/2	0.00	0.903	-0.04, 0.04
Rectum D2cc	-0.01	0.159	-0.02, 0.00	Sigmoid D2cc	-0.02	0.057	-0.04, 0.00	Pelvis vs. pelvis + para-aortic RT	-0.04	0.717	-0.24, 0.17
				Small bowel Dmax	-0.01	0.600	-0.04, 0.03	Small bowel V45Gy	0.00	0.123	0.00, 0.00
				Small bowel V45Gy	0.00	0.069	0.00, 0.00				
				Sigmoid V45Gy	0.00	0.506	0.00, 0.00				

(continued to the next page)

Table 3. (Continued) Multiple linear regression models of symptom scores at each time phase

Parameters	Bowel problems			Bowel bother			Abdominal problems				
	Estimate	p-value	95% CI	Parameters	Estimate	p-value	95% CI	Parameters	Estimate	p-value	95% CI
Late											
3DCRT vs. IMRT	0.16	0.053	0.00, 0.33	3DCRT vs. IMRT	0.20	0.053	0.00, 0.41	3DCRT vs. IMRT	0.17	0.020	0.03, 0.31
Age at diagnosis	0.00	0.531	0.00, 0.01	Age at diagnosis	0.00	0.959	-0.01, 0.01	Sigmoid D2cc	-0.01	0.018	-0.02, 0.00
Non-smoker vs. current smoker	-0.16	0.155	-0.38, 0.06	Non-smoker vs. current smoker	-0.16	0.220	-0.43, 0.10	Small bowel V50Gy	0.01	0.012	0.00, 0.00
Ex smoker vs. current smoker	-0.15	0.211	-0.40, 0.09	Ex smoker vs. current smoker	-0.05	0.733	-0.35, 0.24	Age at diagnosis	0.00	0.569	0.00, 0.01
No EBRT nodal boost vs. EBRT boost	-0.05	0.719	-0.35, 0.24	No EBRT nodal boost vs. EBRT boost	0.15	0.408	-0.21, 0.51	Non-smoker vs. current smoker	-0.12	0.176	-0.29, 0.05
No prior abdominal surgery vs. prior abdominal surgery	0.06	0.597	-0.16, 0.29	No prior abdominal surgery vs. prior abdominal surgery	-0.08	0.587	-0.35, 0.20	Ex smoker vs. current smoker	-0.05	0.586	-0.25, 0.14
FIGO stage 3/4 vs. stage 1/2	-0.01	0.727	-0.04, 0.03	FIGO stage 3/4 vs. stage 1/2	0.02	0.398	-0.03, 0.07	No EBRT nodal boost vs. EBRT boost	0.04	0.718	-0.20, 0.28
Pelvis vs. pelvis + para-aortic RT	0.05	0.609	-0.15, 0.26	Pelvis vs. pelvis + para-aortic RT	0.07	0.580	-0.18, 0.32	No prior abdominal surgery vs. prior abdominal surgery	0.00	0.958	-0.18, 0.19
Small bowel Dmax	-0.02	0.177	-0.05, 0.01	Sigmoid D2cc	-0.02	0.053	-0.03, 0.00	FIGO stage 3/4 vs. stage 1/2	0.00	0.908	-0.03, 0.03
Sigmoid V50Gy	0.01	0.082	0.00, 0.02	Small bowel Dmax	-0.02	0.101	-0.05, 0.00	Pelvis vs. pelvis + para-aortic RT	-0.01	0.906	-0.17, 0.15
Rectum Dmax	-0.02	0.356	-0.06, 0.02	Small bowel V40Gy	0.00	0.220	0.00, 0.00	Small bowel Dmax	-0.02	0.074	-0.05, 0.00
Rectum V50Gy	0.00	0.761	-0.01, 0.01	Rectum V40Gy	0.00	0.065	-0.01, 0.00	Sigmoid V40Gy	0.00	0.208	0.00, 0.00
Small bowel D2cc	0.00	0.308	-0.01, 0.00	Rectum V50Gy	0.00	0.415	-0.01, 0.01	Rectum Dmax	-0.02	0.124	-0.05, 0.01
Sigmoid D2cc	-0.01	0.217	-0.02, 0.00	Rectum D2cc	-0.01	0.217	-0.02, 0.00	Small bowel D2cc	0.00	0.330	-0.01, 0.00
								Rectum D2cc	0.01	0.192	0.00, 0.02

3DCRT, 3D conformal radiotherapy; CI, confidence interval; D2cc, maximum dose to 2cc; Dmax, maximum dose; FIGO, International Federation of Gynecology and Obstetrics; IMRT/VMAT, intensity modulated/volumetric modulated arc therapy; V, volume receiving at least.

Our hypothesis that the improved conformality of IMRT/VMAT would spare adjacent GI OARs was confirmed on validated PROs collected with our POSI questionnaire. These findings were demonstrated despite the inclusion of significantly more para-aortic volumes in the IMRT/VMAT arm which has been shown to increase the risk of acute and late toxicity [18,19].

Improved late GI toxicity with IMRT/VMAT techniques has been shown in prior retrospective studies [20-22]. More recently, a prospective cohort of 44 patients with locally advanced cervical carcinoma were randomized to whole pelvis conventional radiation therapy versus whole pelvis IMRT [23]. In their study, patients treated with IMRT techniques experienced less chronic GI toxicity compared to conventional techniques (13.6% vs. 50%, $p=0.011$). On dosimetric analysis, the mean small bowel V40%, V90%, and V100% were significantly less in patients treated in the IMRT arm. The rectum V40% was also significantly less compared to the conventional radiation arm. This is consistent in our study - treatment with IMRT/VMAT compared to 3DCRT was associated with a lower small bowel V40–45Gy, rectum V40–45Gy, and sigmoid V40–45Gy. These reductions in OAR dose volume histogram (DVH) parameters provides a rational explanation why less toxicity is experienced with these conformal techniques.

On stepwise regression modeling incorporating dosimetric data, increasing small bowel V50Gy was associated with increased symptom scores in late AP. This is consistent with an analysis of EMRABCE data which showed increased grade 2+ diarrhea with larger volumes of V43Gy and V57Gy [24]. Similarly, increasing V40Gy has been found to be associated with chronic GI complications in the post-operative cervical cancer setting [25]. In our study, higher sigmoid brachytherapy D2cc was associated with reduced symptom scores although the absolute estimate was small. It is possible that patients with increased sigmoid dose have anatomy such that the sigmoid occupies the region adjacent to the treatment volume and displaces small bowel, which is inherently more radiosensitive, sparing it from higher doses [26]. The sigmoid is also a mobile intrabdominal structure that is subject to interfractional and intrafractional movement which complicates interpreting dose volume parameters based on the simulation scan [27]. The sigmoid D2cc was not a significant predictor of late diarrhea in the aforementioned EMBRACE study on univariate analysis [24].

There still remains significant heterogeneity in the literature for dosimetric predictors of GI complications. For example, small bowel V15Gy and rectum V5–25Gy have been found to be associated with increase GI toxicity [28,29]. In our study, patients treated with IMRT/VMAT compared to 3DCRT had a higher small bowel V15Gy related to the increased integral dose with more conformal techniques [30]. These lower doses were not found to be significant predictors of toxicity. Dosimetric predictors in cervical cancer are difficult to analyze due to ongoing disease response to RT creating varying anatomical shifts which adds to uncertainty for assessing dose to OARs contoured on the simulation scan. Adaptive RT may present an opportunity to further evaluate dosimetric predictors with tailored plans to the patient's current anatomy at time of each RT fraction [31].

In the adjuvant setting, patients receiving post-operative RT for cervical or endometrial malignancies were found to have significantly worse PROs at week 3 and week 5 of RT if treated with four-field RT [11]. However, there was no significant difference in late GI toxicity, with most GI toxicity improving 4-6 weeks after completion of RT. In a patient population limited to cervical carcinoma, post-operative RT delivered via IMRT compared to 3DCRT significantly reduced the incidence of acute diarrhea from 27.2% to 17.2% and late grade 3+ bowel toxicity from 8.7 to 2% [29].

There are a few hypotheses as to why acute GI toxicity was significantly worse with 3DCRT in the aforementioned post-operative studies, but not in our study evaluating definitive RT. After hysterectomy, the small bowel is displaced lower in the pelvis, increasing the total volume of irradiated bowel, which may increase acute GI toxicity [32]. Furthermore, all patients in our study received a BT boost which has been shown to be associated with acute toxicity [33]. BT has a more limited role in the post-operative setting [34] and BT use was not reported in Klopp et al. [11]. Only 25.5% of patients in Klopp et al. received concurrent chemotherapy which has been shown to be associated with higher rates of acute GI toxicity in the post-operative pelvic RT setting [35]. The majority of patients in both arms of our study received concurrent chemotherapy, thus the radio-sensitizing effects of cisplatin resulted could have negated any significant differences in acute GI toxicity with IMRT/VMAT techniques.

There was no difference in OS, LC, or RC between 3DCRT and IMRT/VMAT arms in our study. This is reassuring as the use of IMRT in gynecological malignancies is increasing since 2004 [36]. Similar survival outcomes among EBRT techniques were also observed in the prospective Ghandi et al. trial and previous retrospective studies [21,23]. A retrospective study by Du et al. [22] reported a significant improvement in five-year progression free survival with IMRT compared to conventional RT (64.9% vs. 44.3%), but no OS benefit was observed. A meta-analysis of n=1,008 patients comparing 3DCRT and IMRT in cervical cancer RT revealed no significant differences in three-year OS and disease-free survival [37].

As there has been a paucity of prospective data, it would be useful to adhere to published intensity modulated contouring guidelines when designing future prospective studies [38]. The EMBRACE II study will be helpful for standardizing intensity modulated techniques with image guided BT in a prospective cohort [5]. Adhering to EMRACE II contouring guidelines can allow dosimetric analyses with multiple institutions and may help determine significant dose volume constraints that correlate with PROs.

It is uncertain whether the results of our study would be replicated in a cohort of patients treated with adjuvant chemoradiotherapy after hysterectomy for high-risk early stage cervical cancer as outlined by Peters et al. [35]. Future work in this select group of patients would help delineate the expected PROs during adjuvant chemoradiotherapy. This information may also help with initial definitive treatment decisions for cervical cancer. For example, if PROs are found to be significantly worse with adjuvant chemoradiotherapy, clinicians may favor upfront definitive chemoradiotherapy to manage patients thought to be at high risk for requiring adjuvant treatment.

This study should be interpreted in the context of its strength and limitations. Limitations of this study include its retrospective nature with the inability to control for confounding variables. There was variation in compliance with completing POSI questionnaires. POSI questionnaires were created by our institution to guide clinical care by using compiled questions from EPIC, PRO-CTCAE, and EORTC. Although the questionnaire is unique to our six cancer centre institution, and this is a limitation of the external validity, our study cohort still represents a population of approximately 5.5 million with a geographical catchment area of 950 square kilometers. The socioeconomic and cultural differences within this large catchment area represents a study strength and our data can be used to compare to other treating institutions in future studies. The contemporary cohort is also a particular strength as all patients in this study were treated with modern image guided EBRT and volume-based

BT techniques with recorded lymph node status which will help correlate our findings with future studies incorporating the new FIGO 2018 staging [39].

In conclusion, this relatively large retrospective cohort study revealed that patients treated with definitive RT (EBRT plus BT boost) for cervical carcinoma have less subacute and late GI toxicity when treated with IMRT/VMAT compared to 3DCRT techniques. Patients treated with IMRT/VMAT had a significantly smaller change in their GI PRO symptom scores compared to baseline in all three GI domains ≤ 12 weeks and > 12 weeks after RT. On multivariable linear regression analysis incorporating dosimetric data, the use of 3DCRT compared to IMRT/VMAT still predicted for increased symptom scores in the subacute BP and late AP domains. The survival and control rates were equivalent for both EBRT techniques and our data supports the ongoing use of IMRT/VMAT in routine practice.

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SUPPLEMENTARY MATERIALS

Table S1

Mean dose volume parameters

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Fig. S1

Prospective Outcomes and Support Initiative (POSI) questionnaire.

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Fig. S2

Dose color wash distributions (3DCRT; VMAT). Blue = 50% isodose. Red = 100% isodose.

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