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Adaptive PET Radiation therapy in patients with Locally Advanced Vulvar Cancer: a Prospective Study

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Abstract

Purpose/Objectives:
In this prospective trial, we aim to determine if FDG-PET/CT based adaptive radiotherapy (ART) improves dosimetry outcomes for patients treated with definitive radiation for locally advanced vulvar cancer (LAVC).

Methods
Patients were enrolled in two sequential IRB-approved prospective protocols for PET/CT ART from 2012-2020. Subjects were planned with pretreatment PET/CT to 45-56Gy in 1.8Gy/fx, followed by a boost to gross disease (nodal and/or primary) to a total of 64-66Gy. Intratreatment PET/CT was obtained at 30-36Gy, and all subjects were replanned to the same dose goals with revised OAR, GTV and PTV contours. RT consisted of either intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT). Toxicity was graded by the CTCAE v5.0. Local control (LC), disease free survival (DFS), overall survival (OS), and time to toxicity were estimated using the Kaplan-Meier method. Dosimetry metrics for OARs were compared using the Wilcoxon signed rank test.

Results

20 patients were eligible for analysis. Median follow up among surviving patients was 5.5 years. LC, DFS, and OS at 2 years were 63%, 43%, and 68%, respectively. ART significantly reduced the following OAR doses: bladder, max dose (dmax) (median reduction (MR) 1.1Gy (IQR 0.48 – 2.3 Gy), p<0.001) and D2cc (MR 1.5 Gy (IQR 0.51 – 2.1 Gy), p<0.001); bowel, dmax (MR 1.0 Gy (IQR 0.11 – 2.9 Gy), p<0.001), D2cc (MR 0.39 Gy (IQR 0.023 – 1.7 Gy), p<0.001), and D15cc (MR 0.19 Gy (IQR 0.026 – 0.47 Gy), p=0.002)); rectal, mean dose (MR 0.66 Gy (IQR 0.17 – 1.7 Gy) p=0.006) and D2cc (MR 0.46 Gy (IQR 0.17 – 0.80 Gy), p=0.006). No patients experienced any grade 3 or higher acute toxicity. There were no reported late ≥G2 vaginal toxicities. Lymphedema at 2 years was 17% (95% CI, 0% - 34%).

Conclusions:
Doses to bladder, bowel, and rectum were significantly improved with ART, though the median magnitudes were modest. Which subjects benefit most from adaptive treatment is a matter for future investigation.

Introduction

Vulvar carcinoma accounts for 6% of all cancers of the female reproductive organs, with 6,330 new cases and 1,560 deaths projected in 2022[1]. For patients with locally advanced vulvar cancer, the mainstay of treatment includes a combination of chemotherapy and radiation therapy, and surgery is reserved for salvage treatment[2]. While radiation techniques have improved over the last few decades, patients often experience toxicities from treatment including damage to the gastrointestinal and genitourinary system, sexual dysfunction, and lymphedema.

Fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) is an important tool for staging, treatment planning, and assessing treatment response following definitive chemoradiotherapy or radiotherapy[3,4]. In head and neck, thoracic, gastrointestinal, and other gynecologic cancers, intra-treatment FDG-PET/CT has been investigated as a method for adaptive radiation planning in order to mitigate toxicities and personalize treatment plans[5-8].

To date, there are no known studies investigating the use of FDG-PET/CT adaptive radiation planning (ART) for patients with locally advanced vulvar cancer. In this prospective

trial, we aim to determine if FDG-PET/CT adaptive radiotherapy improves dosimetric outcomes and treatment toxicity for patients treated with chemoradiotherapy or radiotherapy alone in locally advanced vulvar cancer.

Methods

Patient selection, follow-up, and planning

Patients with 2009 International Federation of Gynecology and Obstetrics (FIGO) stage IB-IVB vulvar cancer who were scheduled for definitive chemoradiation (CRT) or radiation therapy (RT) were enrolled in two sequential Institutional Review Board (IRB)-approved prospective protocols (NCT01908504 and NCT03403465) for PET/CT ART from April 2012 through July 2020. Both studies included the same methodology for mid-treatment evaluation and treatment planning. The only difference between the two approved studies was eligibility for enrollment by treatment site (ie the first protocol included a head and neck cohort [not analyzed in this work] and the second did not). Exclusion criteria included patients who were younger than 18 years old, inability to provide informed consent, uncontrolled diabetes mellitus, pregnancy, those who were breastfeeding, or synchronous primary malignancy.

All enrolled subjects were planned to receive standard institutional regimen or CRT or RT by the recommendations of multi-disciplinary tumor board consisting of radiation oncologists and gynecologic oncologists. RT consisted of either intensity modulated

radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) with 1.8 Gy once daily to a total of 45 – 50.4 Gy and simultaneous integrated boosts (SIB) to involved pelvic or para-aortic (PA) lymph nodes. The primary tumor was treated to 64.4-66.4 Gy with sequential boosts. SIB dose ranged from a total of 64.4 Gy to 66.4 Gy in 25 fractions determined by the treating physician and organ-at risk (OAR) tolerance. OARs of interest included the bladder, bowel, and rectum. Imaging was obtained per protocol, which included FDG-PET/CT scans prior to treatment, an intra-treatment scan at 30-36 Gy for ART, and a post-treatment scan 3 months after completing CRT or RT. The decision for intra-treatment PET at 30-36 Gy was adapted from previously reported data for cervical cancer [5,9-11]. All patients were then re-planned at 30-36 Gy to the same dose goals with revised OAR, gross tumor volume (GTV) and planning target volume (PTV) contours. The GTV primary was defined as gross disease within the vulva. CTV primary included a 10-15mm expansion and areas of high risk disease within the primary site. A 5-7mm expansion was added for a final PTV. A dose of 45-50.4 Gy was prescribed to a PTV_low with a boost to 64-66 Gy to the involved lymph nodes and gross disease.

High dose PTV volumes were only altered in the case when large nodes or gross tumor had significantly reduced in size. The elective volume included the inferior aspect of the vagina, the inguinal lymph node basins, internal and external iliac nodes, and presacral lymph nodes to the level of the bifurcation of the common iliac vessels. PA nodes were included if there was suspicion for involvement based on imaging. The total dose to positive nodes or to elective volume was unchanged in all cases. Planning turn around was between 3-5 business days without any treatment pauses with intent to change to a new plan for the last 5-10 fractions of EBRT in the initial plan, and the subsequent sequential boost plan.

For those patients who received CRT, chemotherapy consisted of 5 weekly cycles of cisplatin during RT at a dose of 40mg/m^2. Chemotherapy was prescribed and given at the discretion of the managing gynecologic oncologist. Patients were seen on a weekly basis in on-treatment visits (OTVs) to discuss management of toxicities and side effects.

Following the completion of treatment, patients were seen in follow up by either the radiation oncologist or gynecologic oncologist every 3 months for 2 years, then every 6 months up to 5 years. Patients were evaluated as needed if there was a new concern. No routine imaging or laboratory tests were performed after the 3 months post-treatment PET/CT unless clinically indicated at the discretion of the evaluating physician.

Imaging details

FDG-PET/CT scans were performed on a Biograph mCT PET/CT System with 128-detector CT (Siemens Medical Solutions, Erlangen, Germany) with a set scanning protocol. Patients were instructed to fast for 4 hours prior to intravenous administration of FDG. The scanning protocol continued if fasting glucose was measured to be less than 200 mg/dL, Exceptions to this were handled at the discretion of the treating radiation oncologist and principal investigator of the study. The FDG was obtained by PETNET Solutions Inc, and the amount administered was 8 to 15 mCi, depending on patient weight (0.14-0.21 mCi/kg). There was then a 1 hour wait before image acquisition following injection. Images were obtained in 16-slice helical scanning mode, 16 x 1.2mm collimation, 0.75 pitch, and 3-mm slice thickness. The PET reconstruction algorithm was ordered subset expectation maximization incorporating time of flight, with a CT matrix size of 512 x 512 and PET matrix size of 200 x 200. CT and PET images were fused directly from the Biograph console.

Statistical Analysis

Patient demographics, FIGO stage at diagnosis, lymph node status and location (pelvis vs PA), tumor histology and grade, radiation prescribed dose, and toxicity during and following treatment as defined by the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 were recorded. Staging was determined by clinical exam and per PET/CT imaging. Local control (LC), disease free survival (DFS), overall survival (OS) were estimated using the Kaplan-Meier method. LC was defined as freedom from recurrence within the treatment field. Further workup and biopsy confirmation was only performed if there was clinical suspicion for recurrence. DFS was defined as freedom from recurrence at any site or death from any cause. OS was defined as death from any cause. All time-to-event endpoints were measured from the end of RT; censoring was at time of last follow-up. Late toxicity was calculated as a cumulative incidence at time points after completion of radiation therapy.

Dosimetry metrics of OARs of interest including bladder, bowel, and rectum were collected for pre- and intra-treatment plans. Dosimetry metrics for OARs in the un-adapted vs the adapted intra-treatment plan were compared using the Wilcoxon signed rank test. It was

determined that assuming that a clinically relevant dosimetric benefit would be achieved when >66% of the adaptive plans were superior to the initial plans, a sample size of 40 would be sufficient achieve a significance test of < 0.05 (specifically if 26/40 plans are dosimetrically superior, an exact two tailed test results in a p value of 0.038). The study was closed prior to 40 subjects due to slow accrual. All statistics were performed using SPSS v27 and R v3.6.0. Definition of significance was defined as $p< 0.05$. Adjustments for multiple comparisons was not applied due to the rarity of the malignancy.

Results

Patient and treatment characteristics

22 patients were enrolled, and 20 were eligible for analysis. Median follow up among surviving patients was 5.5 years. **Table 1** summarizes patient demographics and disease characteristics. The majority had FIGO stage II vulvar cancer (8 of 20 patients, 40%). 95% of patients received concurrent chemotherapy with weekly cisplatin (19 of 20 patients). The median dose to the tumor volume was 65.5 Gy. All patients completed pre- and intra-treatment FDG-PET/CT scans. The median time between pre- and intra-treatment PET was 38 days. Cumulative incidence of LC, DFS, and OS (**Figure 1**) at 2 years were 63% (95% CI 41-85%), 43% (95% CI 21-66%), and 68% (95% CI 47-89%), respectively. Mean reduction of volume of high dose PTV from pre- to mid-treatment planning was 65.9cc (median, 53.24, IQR: 19.09 – 84.78cc). Mean reduction of volume of low dose PTV from pre- to mid-treatment planning was 129.5cc (median, 48.74, IQR: 26.41 – 136.45cc). Individual reduction of PTV volume by patient is summarized in **Supplemental Table 1**.

Toxicities

45% of patients experienced at least grade 2 (G2) acute gastrointestinal (GI) toxicity. 20% of patients experienced at least grade 2 (G2) acute genitourinary (GU) toxicity. No patients experienced acute vaginal toxicity. No patients experienced any grade 3 or higher acute toxicity. G2 or more late GI toxicity at 2 years was 5% (95% CI, 0% – 15%). G2 or more late GU toxicity at 2 years was 11% (95% CI, 0% - 26%). There were no reported late ≥G2 vaginal toxicities. Lymphedema at 2 years was 17% (95% CI, 0% - 34%). Cumulative incidence of late GI toxicity,

GU toxicity, and lymphedema is displayed in **Figure 2**. All patients (100%) experienced G2 skin toxicity around the tumor site (moist desquamation) within the acute setting, as expected in this treatment. No patients experienced a treatment break and toxicity was conservatively managed as needed.

Dosimetric Outcomes

ART significantly reduced all dosimetric constraints for the bladder, including max dose (Dmax) (median reduction 1.1Gy (IQR 0.48 – 2.3 Gy), p<0.001), mean dose (Dmean) (median reduction 0.91 Gy (IQR 0.09 – 1.1 Gy), p=0.001), D2cc (median reduction 1.5 Gy (IQR 0.51 – 2.1 Gy), p<0.001). For bowel, all dosimetric constraints were significantly reduced by ART. Dmax (median reduction 1.0 Gy (IQR 0.11 – 2.9 Gy), p<0.001), D2cc (median reduction 0.39 Gy (IQR 0.023 – 1.7 Gy), p<0.001), and D15cc (median reduction 0.19 Gy (IQR 0.026 – 0.47 Gy), p=0.002)) were the most reduced in order of magnitude. For rectum the Dmean (median reduction 0.66 Gy (IQR 0.17 – 1.7 Gy) p=0.006), Dmedian (median reduction 0.43 Gy (IQR -0.052 – 1.61 Gy), p=0.007) and D2cc (median reduction 0.46 Gy (IQR 0.17 – 0.80 Gy), p=0.006) were significantly reduced with ART. Rectal Dmax, V45, and V50 were not significantly changed with ART. A summary of dosimetric outcomes is reported in **Table 2.** The absolute magnitude of dose by each constraint was recorded and reported in **Supplemental Table 2**. Due to the small numbers within this study, further analysis associating dose and patient toxicity was not possible. An example of before and after PTV volumes based on ART is illustrated in **Figure 3**.

Discussion

In this prospective study involving patients with locally advanced vulvar cancer treated with chemoradiotherapy or radiotherapy alone, dose to normal organs is significantly improved with acceptable level of toxicity using ART. Survival outcomes, including local control, is similar or improved compared to historical experiences in vulvar cancer[2,12-15]. In a phase II study from the Netherlands which treated locally advanced vulvar cancer with definitive chemoradiation, local control was 42% at 2 years[15]. Although surgery has been a mainstay of treatment for vulvar cancer, results of effective chemoradiation and radiation treatments are promising. In an National Cancer Database (NCDB) analysis of 2,046 women, the authors find

that outcomes among patients who receive doses more than 55 Gy with chemotherapy were not significantly different from those who receive preoperative radiation or chemoradiation (HR= 1.139; 95% CI: 0.969-1.338; p= 0.116)[12]. Primary chemoradiation that achieves a dose higher than at least 55 Gy may provide adequate disease control[12]. However, toxicities from treatment may be debilitating to patients and the current study aims to provide effective doses of radiation treatment, while minimizing dose to normal organs.

While technology improves with treatment planning, including the use of Intensity-Modulated Radiation Therapy (IMRT), doses needed for effectively disease control are able to be administered more safely. IMRT is an advanced method of administering radiation therapy that modulates the intensity of radiation from the beam during the path of radiation. In the setting of gynecologic malignancies, the emerging use of IMRT has provided excellent tumor control with sparing of the normal pelvic organs[16,17]. In a comparative analysis by Beriwal et al., IMRT was superior to 3D conformal treatment in reducing dose to OARs and toxicity for patients with vulvar cancer[18]. Both GOG 101 and GOG 205 sought out to treat locally advanced disease with neoadjuvant chemoradiation, with aim of converting to resectable disease[13]. While GOG 205 was able to achieve dose escalation to 57.6 Gy in 1.8 Gy per fraction, and improved outcomes in pathologic complete response in patients who were initially unresectable, IMRT was not allowed on study. In our present study, radiation techniques included both IMRT and ART, as well as dose escalation higher than GOG 205. While it is possible that the use of IMRT rather than 3D RT planning may be a reason for ongoing improvement in toxicity, the use of ART may be important when dose-escalating. In a retrospective study by Rao et al., 39 patients with vulvar cancer were treated with IMRT, either postoperatively, preoperatively or definitively, patients had limited grade 3-4 toxicity. It is of note, however, that the local control and OS for the patients who were treated with definitive treatment at 3 years was 42% and 49%, which is notably lower than historical controls and our current study[19]. In the present study, only 1 patient experienced a late grade 3 gastrointestinal toxicity and 1 patient experienced grade 3 genitourinary toxicity. By nature of this study as a single arm, feasibility study, without a direct comparison as a randomized trial, we are unable to draw firm conclusions that ART has improved toxicity. However, the current study has achieved a relatively higher local control, while also administering high doses of definitive chemoradiation with acceptable toxicities.

In the present study, we find that multiple dosimetric parameters improved and were statistically significant in the following ART. In a phase II trial evaluated cisplatin and gemcitabine concurrent with IMRT for locally advanced vulvar cancer (GOG 0279), which has recently closed to accrual, constraints for bowel, rectum, and bladder were specified as follows: < 30% of the bowel to receive ≥ 40% of the dose, Dmax ≤ 51 Gy; < 80% of rectum to receive ≥ 40 Gy; Dmax < 65 Gy; and < 50% of bladder to receive ≥ 45 Gy; Dmax ≤ 65 Gy[20]. In our study, we aimed to achieve similar goals while balancing the need to adequately cover gross disease. With many of our patients enrolled in this study, we were able to achieve reduction of dose to surrounding structures using adaptive planning safely, without apparent compromise of local control.

ART is a method that is commonly used in radiotherapy when treating a volume disease that may change in size as a result of treatment response[21]. Per the most recent consensus guidelines for contouring gynecologic malignancies, there is explicit recommendation that adaptive planning should be considered when there are significant clinical changes during the treatment.[22] Due to the rarity of vulvar cancer treated with definitive chemoradiation or radiation, there is limited knowledge on the use of ART in this setting. One retrospective study by Abuhijla et al showed that out of 22 patients with non-operable vulvar cancer at their hospital, 13 plans required ART, with the change of tumor volume ranging from 3cc to 41cc[23]. This study differs from the present study as this group did not routinely use PET/CT for staging or planning, and did not report dose changes to OARs. To date, our study is the first to prospectively assess the dosimetric constraints to OARs and toxicity using PET/CT ART. Although the changes are modest in the current study, the dose reduction of normal organs may be clinically impactful in long term follow up.

This study has several limitations. Given the rarity of this disease, the smaller sample size and limited follow-up result in low statistical power to explore associations between baseline characteristics and toxicity and time-to-event endpoints. Future studies should include analysis of predictors of response during intra-treatment PET on clinical outcomes, such as local control and survival. In addition, future studies would need larger sample sizes in order to further correlate toxicity to dosimetric constraints.

Conclusion

In this prospective study, doses to bladder, bowel, and rectum were significantly reduced, though the median magnitudes were modest. Which subjects benefit most from adaptive treatment is a matter for future investigation. Treatment overall was well tolerated. Local control is similar to historical experiences, and efforts are indicated to improve on these results. PET/CT ART may be considered a reasonable option for the treatment of LAVC in future studies, and may allow for dose escalation or the inclusion of novel radiation sensitizers, while limiting potential toxicities.

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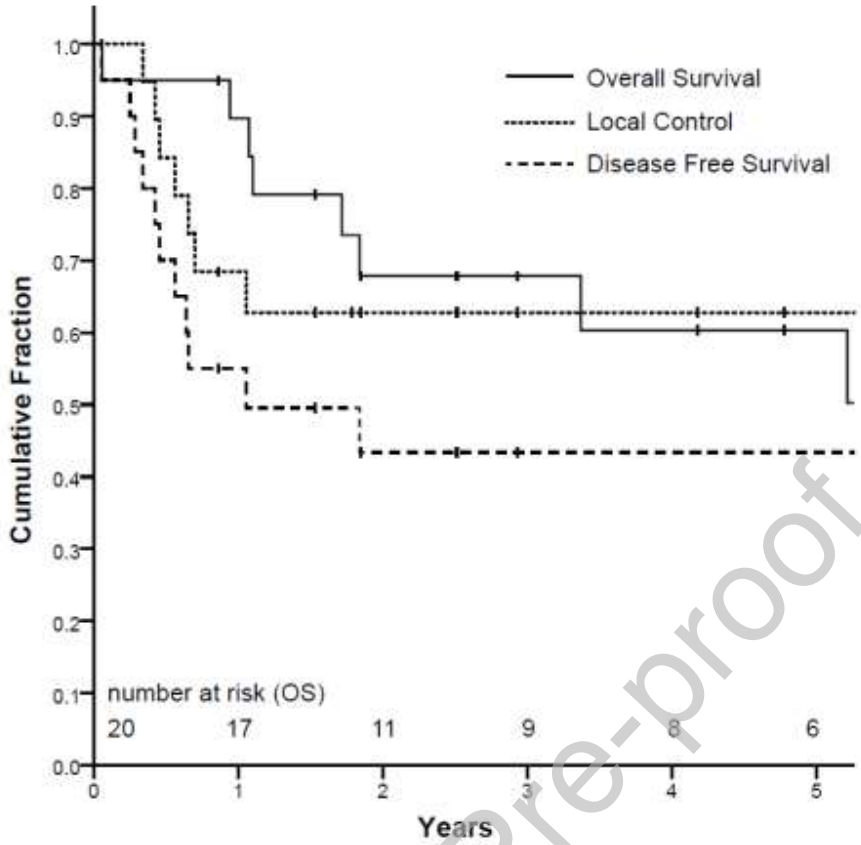

Figure 1: Kaplan Meier Survival Curves

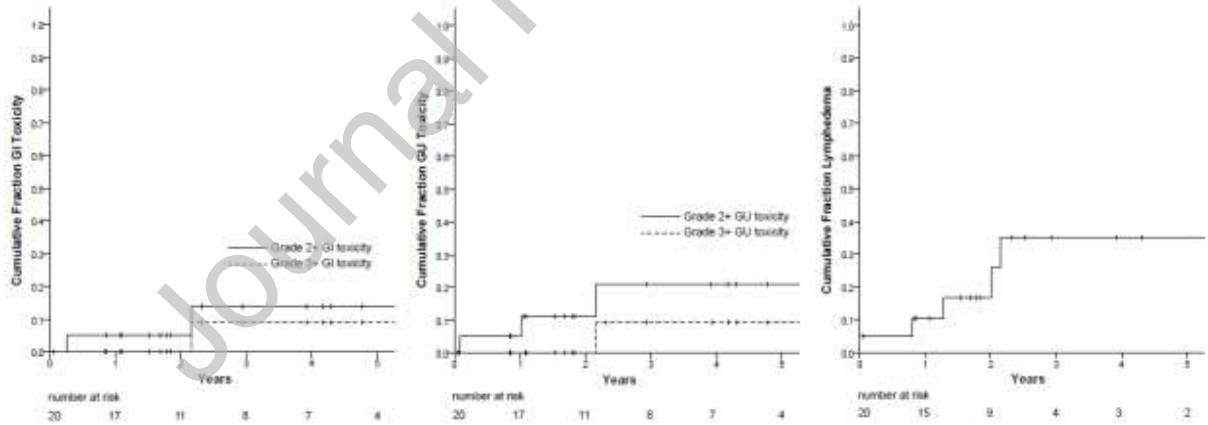

Figure 2: Cumulative Incidence Plots of Toxicities

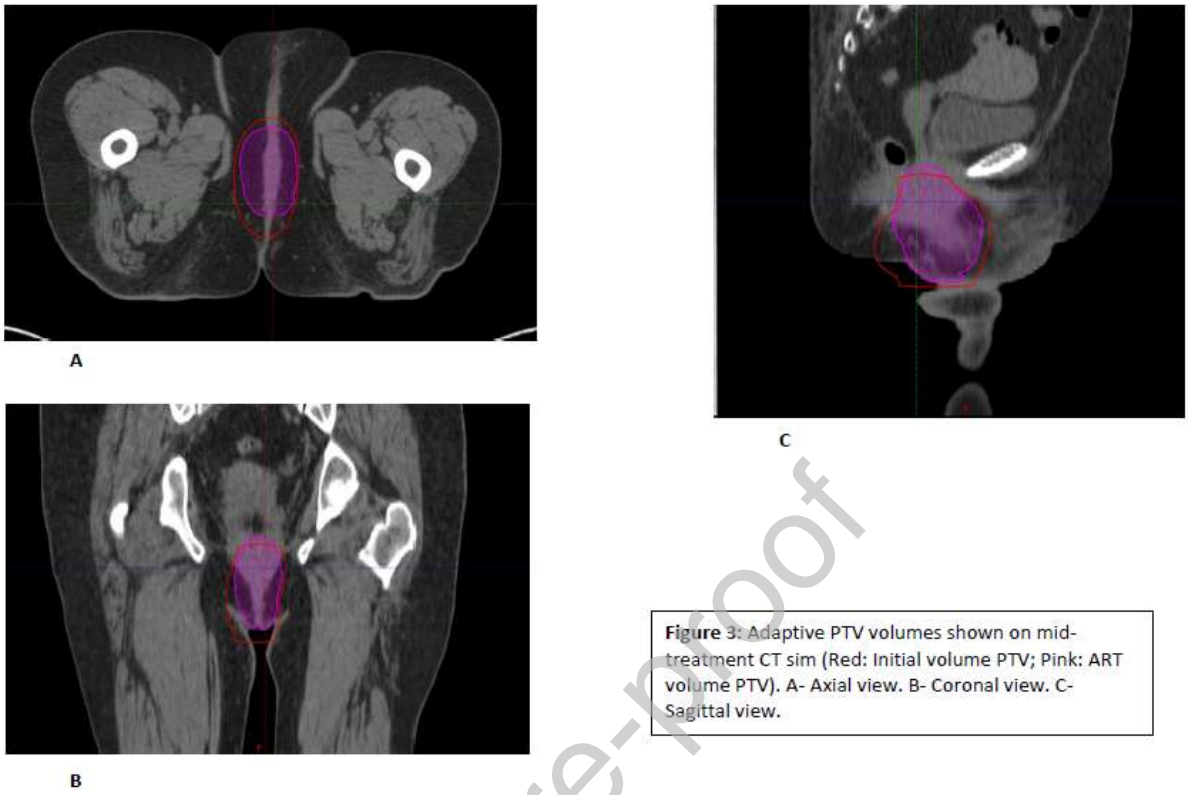

Figure 3: Adaptive PTV volumes shown on mid-treatment CT sim (Red: Initial volume PTV; Pink: ART volume PTV). A- Axial view. B- Coronal view. C- Sagittal view.

Figure 3: Adaptive PTV volumes shown on mid-treatment CT sim (Red: Initial volume PTV; Pink: ART volume PTV). A- Axial view. B- Coronal view. C- Sagittal view.

		N	%
FIGO stage*	IA	0	0
	IB	2	10
	II	7	35
	IIIA	3	15
	IIIB	2	10
	IIIC	2	10
	IVA	4	20
	IVB	0	0
LN status	LN -	6	30
	Pelvic LN +	13	65
	PA LN +	0	0
	Unknown	1	5
Histology	SSC	19	95
	Adenocarcinoma	1	5

Grade	1	1	5
	2	2	10
	3	3	15
	n/a	14	70
Chemotherapy	Yes	19	95
	No	1	5
		Median	Range
	Age at diagnosis	64	48 - 77
	Dose to primary, Gy	50.4	45 - 56
	Boost dose, Gy	16	10 - 20

Abbreviations: LN= lymph nodes; PA= para-aortic; SSC= squamous cell carcinoma;

*2018 FIGO staging used

Table 1: Baseline Patient Demographics, N=20

Table 2: Dosimetric constraints and reductions

OAR	Dosimetric constraint	p- value	Median reduction (Gy)	Interquartile Range (IQR) (Gy)
Bladder	Dmax	<0.001	1.1	0.48 - 2.3
	Dmean	0.001	0.91	0.09 - 1.1
	Dmedian	0.007	0.64	0.08 - 1.1
	D2cc	<0.001	1.5	0.51 - 2.1
	V56	0.010	0.01	0.003 - 0.04
Bowel	Dmax	0.001	1.0	0.11 - 2.9
	Dmean	0.011	0.06	-0.005 - 0.49
	Dmedian	0.039	0.03	-0.007 - 0.46
	D2cc	0.001	0.39	0.023 - 1.7
	D15cc	0.002	0.19	0.026 - 0.47
	V15	0.012	0.002	-0.0002 - 0.032
	V45	0.015	0.013	-0.001 - 0.12
Rectum	Dmax	0.083	0.49	0.045 - 1.13
	Dmean	0.006	0.66	0.17 - 1.7
	Dmedian	0.007	0.43	-0.052 - 1.61
	D2cc	0.006	0.46	0.17 - 0.80
	V45	0.074	0.092	-0.0018 - 0.02
	V50	0.053	0.012	-0.0023 - 0.03