

## Radiotherapy Dose Escalation with Concurrent Chemotherapy Improves Outcome in Locally Advanced Cervix Carcinoma

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### Abstract

**Background:** To evaluate radiotherapy dose escalation using volumetric modulated arc therapy (VMAT) and image guided radiotherapy (IGRT) with concurrent chemotherapy in locally advanced cervix cancer (LACC) and compare it with conventional radiation therapy (CRT) in terms of the toxicity and clinical outcomes.

**Methods and Materials:** Data base was reviewed for all LACC patients treated either by conventional radiation therapy or dose escalation volumetric modulated arc therapy, with concurrent weekly Cisplatin 40 mg/m<sup>2</sup> followed by high dose rate brachytherapy. The primary and secondary endpoints were toxicity, disease-free survival and overall survival respectively.

**Results:** Of 60 patients, 40 patients received CRT and 20 received VMAT. The median follow-up time in the CRT arm was 47 months (11-89), and 35 months (13-47) in the VMAT arm. Hemoglobin toxicity (Grade I-II) was encountered in 97.5% and 90% (p=0.03) while (Grade I-III) Leukopenia was 90% and 70% (p=0.02), respectively. There was no grade 3 or 4 gastrointestinal or genitourinary (GI or GU) toxicity. At 36 months, disease-free survival was 45% in the CRT group versus 75% in the VMAT group (p=0.03), and overall survival was 65% in the CRT group versus 85% in the VMAT group (p=0.8).

**Conclusion:** VMAT is associated with significantly less toxicity and comparable or even better clinical outcome compared with CRT. Further studies with larger sample sizes and longer follow-up times are warranted to justify its use in routine clinical practice.

**Keywords:** VMAT; Cervix cancer; Radiotherapy; Dose escalation treatment; Toxicity; Clinical outcome

### Introduction

Cervical cancer is a major world health problem for women. The global yearly incidence of cervical cancer in 2012 was 528,000; the annual death rate was 266,000 [1]. It is the fourth most common cancer in women worldwide [2,3], with 85% of cases occurring in developing countries, where cervical cancer is a leading cause of cancer death in women [1,4].

Concurrent cisplatin-based chemoradiation in combination with brachytherapy has been established as the standard treatment for locally advanced cervical carcinoma (LACC) [5]. However, the survival rates remain modest, with a 5-year disease-free survival (DFS) and overall survival (OS) of approximately 50% to 60%, respectively and 5-year pelvic failure rates approximating 30% with a combined modality approach [5].

Traditionally, whole pelvic radiation therapy with either a 2-field or a 4-field technique has been used, but it is associated with significant

rates of gastrointestinal (GI) and hematologic toxicities [5,6]. Dosimetric studies have shown that intensity modulated radiation therapy (IMRT) can reduce bowel, rectal, bladder, and bone marrow dose [7-9], and early clinical studies have demonstrated lower rates of GI, genitourinary (GU), and hematologic toxicity compared with conventional techniques [7,10,11]. Yet, although clinical outcome has been reported to be comparable to that of conventional techniques [12-14], prospective studies comparing IMRT with conventional techniques for LACC are lacking.

In 2011, when we modified our radiation protocol, the goal was to intensify the radiation dose and volume for these typical large cancers and shorten the overall treatment time by integrating the boost (nodal and parametria/primary) within the usual 25 fractions of radiotherapy over 5 weeks. VMAT patients had a larger target volume by moving the top border (L3/L4) to systematically cover nodes around aortic bifurcation as compared to standard L4/L5 border for our historic 3DCRT patients.

We have presented our initial experience of VMAT to escalate radiation dose by simultaneous integrated boost (SIB) to gross tumor (primary and nodal) with weekly cisplatin chemotherapy and

compared this with 3DCRT in terms of clinical toxicity with emphasis on hematologic toxicity and it was feasible [15]. Here we compared toxicity and survival outcomes between the 2 arms as primary and secondary objectives. This is a feasibility report for intensified radiotherapy with a longer follow-up before subjecting this approach to a randomized trial.

## Methods and Materials

### Patient characteristics

The medical records of women receiving concurrent chemo radiation therapy for locally advanced cervical cancer (LACC) between 2005 and 2008 were reviewed for CRT (40 patients) and database was reviewed for patients treated by VMAT/IGRT during 2011 and 2012 (20 patients). Patients who had para-aortic lymph nodes radiotherapy or required blood transfusion prior to radiotherapy were excluded.

### Study design

Patients in both arms received external beam radiation therapy (EBRT) to the pelvis with concurrent administered intravenously cisplatin once a week at a dose of 40 mg/m<sup>2</sup>. After the completion of EBRT, all patients then received CT-based image-guided high-dose-rate (HDR) intra cavitary radiation therapy (ICRT), 7 Gy times three to CRT arm versus 6 Gy times four to VMAT arm. All HDR treatments were given twice a week aiming to complete both external and brachytherapy treatments within an overall time of 56 days.

### Radiation therapy planning

IMRT, conventional radiation therapy and brachytherapy planning details were discussed in elsewhere [15].

**Follow-up and evaluation of toxicity:** After completion of treatment, patients in both arms were followed up every three month for first two years and then every six months two years after then once per year. CT scan of the abdomen and pelvis or whole body positron emission tomography/CT was obtained at the 3-month follow-up visit and then at 6-month intervals on the basis of on clinical suspicion. Patients in both arms were assessed throughout treatment and until 90 days after completion of treatment for acute toxicity then after 90 days, late toxicities were graded during follow-up according to the radiation therapy oncology group criteria (RTOG) [16].

**Evaluation of outcome and statistics:** The primary endpoint is the treatment toxicity and the secondary end point was disease free survival (DFS) which was measured from the initiation of concurrent chemo radiation therapy to the first event of local failure, distant metastasis, or death and overall survival (OS) was measured from the initiation of concurrent chemo radiation therapy to death of any cause. The DFS and OS were estimated by the Kaplan-Meier method [17].

A Fisher's exact test was used to compare toxicity between arms. SPSS Software, version 16.0 (SPSS Inc, Chicago, IL), was used for all data analyses, and all P values were based on a 2-sided hypothesis.

## Results

### Patients

Table 1 summarizes patient's characteristics which were discussed previously [15]; the histology distribution was squamous cell histology in 90% and 95% of CRT and VMAT respectively (p=0.6). Grade III was common (40%) in CRT while grade II (60%) in VMAT (p=0.1).

	CRT	VMAT	P-value
Age	Mean 46 (30-63)	Mean 47 (33-67)	-
<b>Stage</b>			0.002
I	17.50%	35%	
II	75%	30%	
III	7.50%	35%	
Tumor size	5 cm (2 cm to 8 cm)	5 cm (2 cm to 10 cm)	-
Gross pelvic nodes	5 (12.5%)	13 (65%)	0.001
Blood transfusion during therapy	55%	45%	0.5
<b>Pathology types</b>			0.6
Squamous	90%	95%	
others	10%	5%	
<b>Tumor grade</b>			0.1
I	25%	20%	
II	35%	60%	
III	40%	20%	

Chemotherapy completed per protocol	90%	95%	0.4
All radiotherapy completed in predefined 56 days	78%	90%	0.02

**Table 1:** Baseline and treatment parameters.

**Toxicity**

Treatment toxicity was recorded according to RTOG criteria and was discussed previously [15]. The difference for this hemoglobin toxicity was statistically significant in favor of VMAT with p value 0.03. Higher incidence of leukopenia in CRT arm was statistically significant with a p value of 0.02. There was no acute G3 or G4 gastrointestinal or urogenital toxicity in both arms.

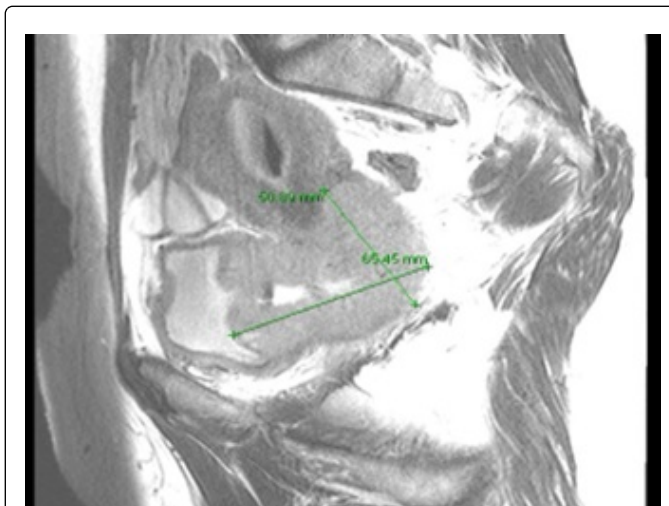
Furthermore, there was no statistical difference in number of grade 2 or below acute gastrointestinal and urogenital toxicity. With a median follow-up of 47 months (11-89) for CRT cohort and 35 months (13-47) for VMAT cohort, there is no late grade 3-4 toxicity in either arm.

**Outcomes and patterns of failure**

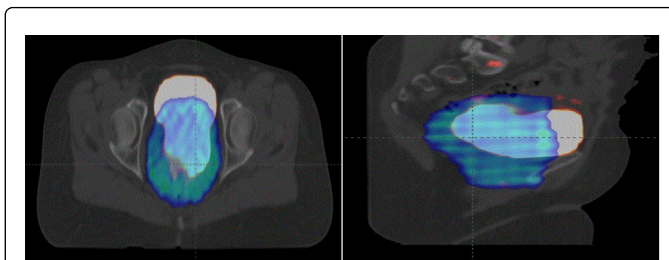
After 3 months of treatment, the complete response was 50% in CRT while 95% in VMAT (p=0.001). After 6 and 12 months, the complete response was 50% in CRT while 90% in VMAT (p=0.003). After 24 months, the complete response was 47.5% in CRT while 80% in VMAT (p=0.01).

Figures 1-8 showed the pre & post treatment imaging with PTV50 for two patients showed complete response. At 36 months, DFS was 45% in the CRT arm versus 75% in the VMAT arm (p=0.03), and OS was 65% in the CRT arm and 85% in the VMAT arm (p=0.8), Figures 9 and 10.

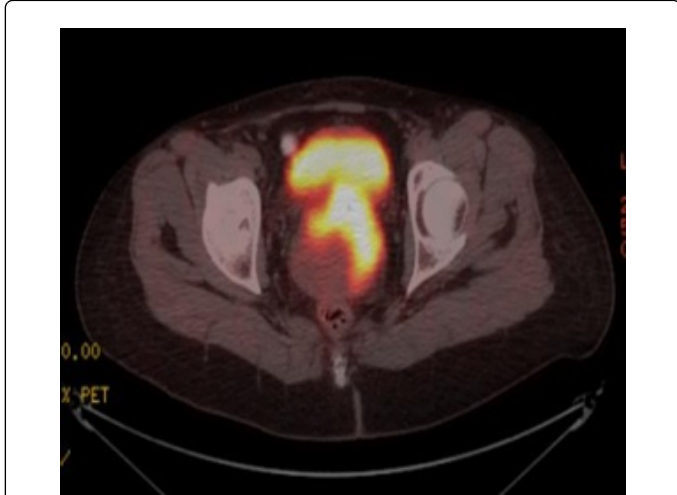
The median progression free survival was 24 months in CRT arm but was not reached in VMAT arm. All failure cases were loco regionally and distantly in CRT arm (52.5%) while one case (5%) was failed loco regionally and distantly and the rest of cases (15%) were distantly only in VMAT arm (p=0.03) (Table 2).



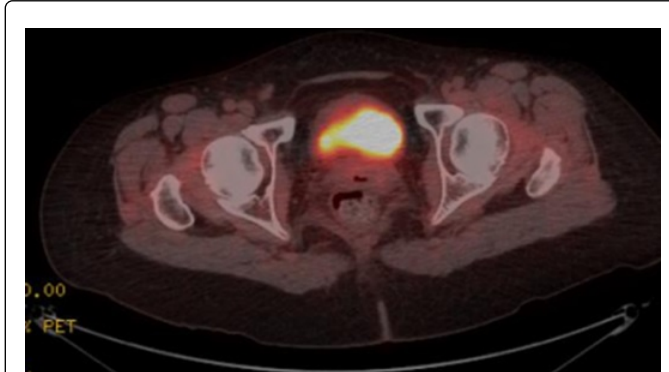
**Figure 2:** MRI pelvis pre treatment.



**Figure 3:** Dose distribution displayed on fused planning CT scan with PET/CT in color wash for PTV50.



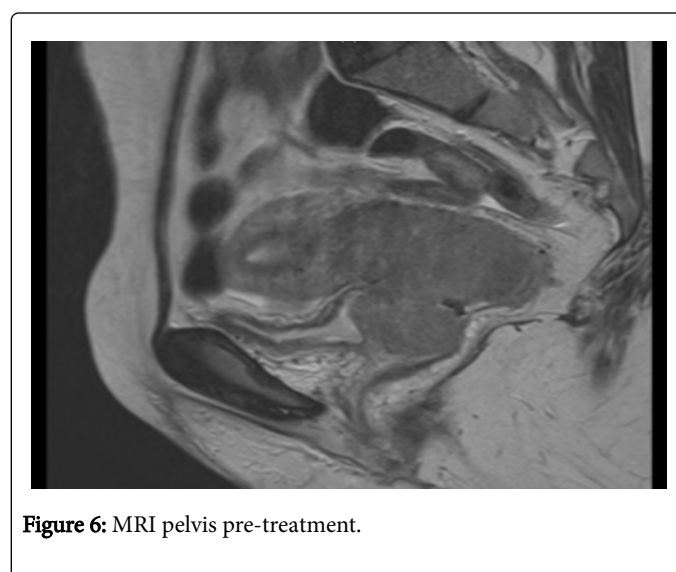
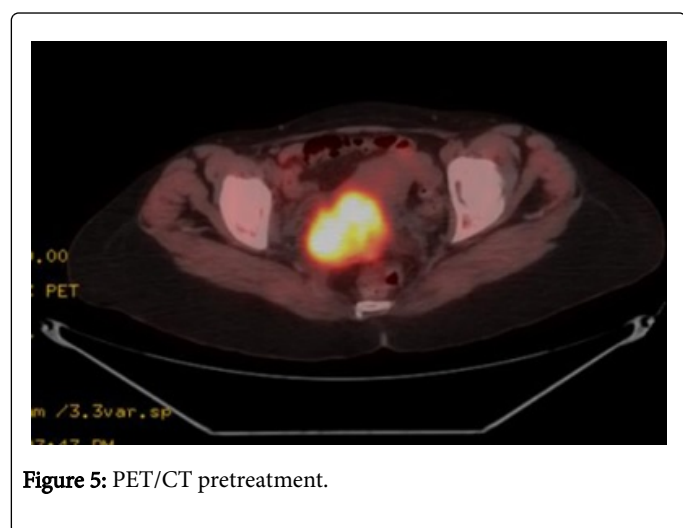
**Figure 1:** PET/CT pretreatment.

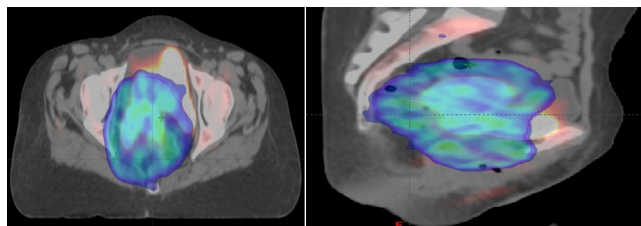


**Figure 4:** PET/CT 3 months post treatment with CR.

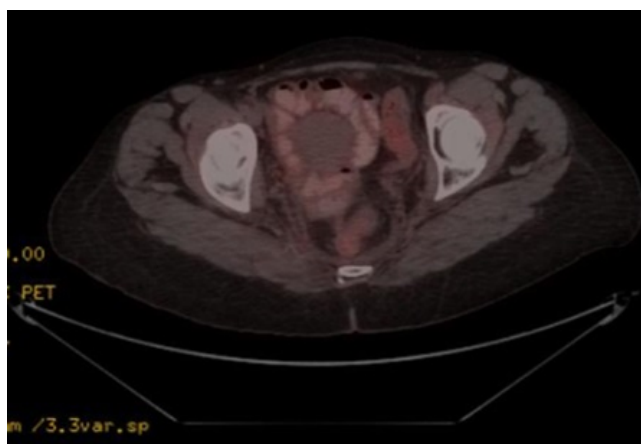
	CRT	VMAT	P-value
<b>Hemoglobin toxicity</b>			
Grade I-II	97.50%	90%	0.03
BMH (g/l)	121.4	115	
AWH (g/l)	115.7	109	
MDH (g/l)	20	17	
<b>WBCs toxicity</b>			
Grade I-III	90%	70%	0.02
BMW (×109/l)	7	7	
AWW (×109/l)	4	5	
MDW (×109/l)	4.7	5.4	
<b>GI toxicity</b>			
Grade I-II	67.50%	40%	0.1
<b>GU toxicity</b>			
Grade I-II	35%	20%	0.2
<b>Complete Response</b>			
3 months	50%	95%	0.001
6 months	50%	90%	0.003
12 months	50%	90%	0.003
24 months	47.50%	80%	0.01
CRT: Conformal Radiotherapy; VMAT: Volumetric Arc Therapy; HB: Hemoglobin; BMH: Basal Mean Hemoglobin; AWH Average Weekly Hemoglobin; MDH: Maximal Drop Of Hemoglobin; WBC: White Blood Cells; BMW: Basal Mean WBC; AWW: Average Weekly WBC; MDW: Maximal Drop Of WBC; GI: Gastrointestinal; GU: Genitourinary.			

**Table 2:** Radiation toxicity and response.

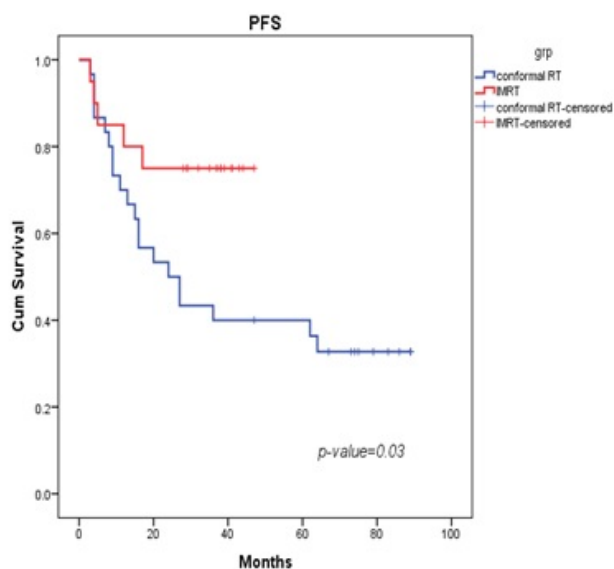




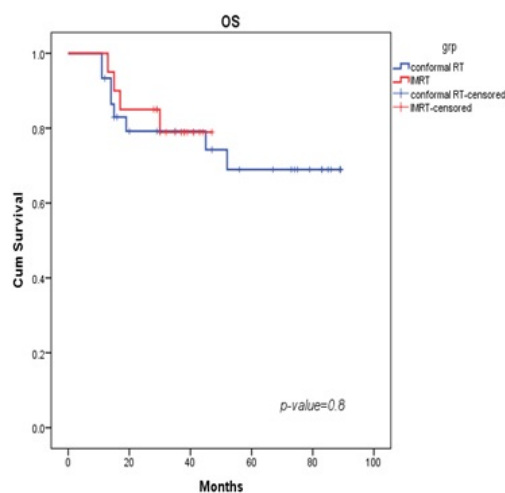
**Figure 7:** Dose distribution displayed on fused planning CT scan with PET/CT in color wash for PTV50.



**Figure 8:** PET/CT 3 months post treatment with CR.



**Figure 9:** Progression free survival curve.



**Figure 10:** Overall survival curve.

## Discussion

Conventional radiation therapy remains the gold standard for LACC. Preliminary studies have shown reduced toxicities and comparable clinical outcomes with IMRT compared with CRT, and despite a lack of prospective randomized data to support its use, the use of IMRT for gynecologic malignancies, including LACC, has increased over the last decade [18].

Our study aimed to evaluate the toxicity and clinical outcomes of radiotherapy dose escalation to gross tumor by simultaneous integrating boost within conventional 25 fractions (SIB) using volumetric modulated arc therapy (VMAT) in locally advanced cervix cancer (LACC).

Our study has shown that despite larger volume treated (superior border at L3/L4 for VMAT and L4/L5 for 3DCRT group) to a higher radiation dose, toxicity and clinical outcomes were significantly better with bone marrow-sparing VMAT approach. It is also to be noted that there were more patients with advanced Stage III cancers with higher proportion of pelvic nodes in VMAT arm. Advances in imaging, in particular with FDG-PET and MRI, have also brought about changes in the treatment of cervical cancer by helping to better define areas of disease.

The results of previous retrospective studies 12-14 support our findings. Rose et al. [19] reported 3-year OS of 51.4% to 61.4% for 47 cervical cancer patients treated with IMRT for stage IIB-IIIB disease. Du et al. [14] reported a significant improvement in 5-year progression-free survival rates with IMRT but no improvement in OS in a retrospective comparison of IMRT and conventional radiation therapy.

Gandhi et al. [20] reported a DFS (60% in IMRT vs 79.4% in CRT) and OS (85.7% in IMRT vs 76% in CRT) were not statistically different between arms at 27 months, but in as much as the median time to recurrence may be as long as 36 months, longer follow-up times may be useful in clarifying this discrepancy.

In our study, DFS (75% in VMAT vs 45% in CRT) was statistically different between arms at 36 months (p=0.03) while OS (85% in VMAT vs 65% in CRT) was not (p=0.8), but longer follow-up times may clarify this discrepancy. Table 4 provides a review of prior studies for the purpose of comparison, the 3 earlier studies, like the study reported here, and there is only one randomized prospective trial [20].

Reference	No. (No. of IMRT patients)	Study type	Median follow up	Grade ≥ 2	Grade ≥ 3	Grade ≥ 2	Grade ≥ 3	Clinical outcome
			(IMRT vs. CRT)	GI toxicity	GI toxicity	GU toxicity	GU toxicity	(IMRT vs CRT)
				(IMRT vs. CRT)	(IMRT vs. CRT)	(IMRT vs. CRT)	(IMRT vs. CRT)	
Du et al. [14]*	122 (60)	Retrospective	47 (6-68)	17.6% vs. 31.60% (p=0.03) Z	5.3 vs. 8.30% (p=0.03) Z	14.1 vs. 38.30% (p=0.001) Z	7.1% vs. 18.30% (p=0.001) Z	5 year PFS 64.9% vs. 44.3% (p=0.03) 3 year OS 90.7 vs. 91.3 % (NS)
Kidd et al. [13]	452 (135)	Retrospective	52 (5-117)	NA	5.18% vs. 10.72% y, Z	NA	0.74% vs. 6.3% y, Z	No difference in RFS; OS better in IMRT arm (p<0.0001)
Thawani et al. [21]	96 (39)	Retrospective	NA	NA	4% vs. 21% (P<0.01)	NA	2% vs. 11% (p<0.01)	NA
Gandhi et al. [20]	44 (22)	Prospective randomized	21.6 (7.7-34.4) vs. 21.7 (10.7-37.4)	31.8% vs. 63.60% (p=0.034) x	4.5% vs. 27.30% (p=0.047) x	23.8% vs. 31.80% (p=0.40) x	0% vs. 13.6% (p=0.125) x	At 27 months, DFS 60% vs. 79.4% (p0.651), OS 85.7% vs. 76% (p0.645)
Present series	60 (20)	Retrospective	35 ( 13-47 ) vs. 47 (11-89)	40% vs. 67.50% (p=0.1)	NA	20% vs. 35% (p=0.2)	NA	At 36 months, DFS was 45% vs 75% (p .03), OAS 65% vs 85% (p 0.8)
Abbreviations: CRT = conventional radiation therapy; DFS = disease-free survival; GI = gastrointestinal; GU = genitourinary; IMRT = intensity modulated radiation therapy; NA = not applicable; NS = not significant; OS = overall survival; PFS = progression-free survival; RFS = recurrence free survival. * Midline blocks were used in the conventional radiation therapy arm and reduced field IMRT was used. Y= Chronic toxicity per Radiation Therapy Oncology Group criteria. Z =Toxicity graded per Radiation Therapy Oncology Group criteria.								
X=Toxicity graded per Common Terminology Criteria for Adverse Events, version 3.0.								

**Table 4:** Clinical outcomes and toxicity of selected studies comparing IMRT versus conventional radiation therapy in locally advanced cervical carcinoma.

Notably, although the overall survival outcomes are not statistically different between arms, we did observe a significant benefit in regard to toxicity and progression free survival. Another advantage of our study is the use of image guidance. The main limitation of our study is a relatively modest sample size and limited times of follow-up. The lower rates of hematologic toxicity with VMAT in our study could be related to the use of bone marrow-sparing techniques, as has been suggested by recent studies [19]. Although the issue has been debatable until now, we seem to be progressing toward a standardized approach to IMRT for intact cervical cancer patients. The results of our study should lend support for the pursuit of further studies and open avenues for prospective multi institutional studies to further define the role of IMRT in LACC.

## Conclusion

In our experience of 60 women with LACC treated with chemoradiation therapy, VMAT resulted in a lower rate of hematological toxicity and comparable clinical outcome than CRT. Further studies with larger sample sizes and longer follow-up times are needed to define the role of VMAT in the management of LACC.

## Compliance with ethical standards

This study has been approved by the institutional ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to therapy; however, for retrospective review of data with less than minimal risk to the patients, no consent was

required by the ethics committee. All authors declare that there is no conflict of interest.

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