



# A dosimetric and radiobiological impact of VMAT and 3DCRT on lumbosacral plexuses, an underestimated organ at risk in cervical cancer patients

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## ABSTRACT

**Background:** The purpose of this study was to evaluate dosimetric and radiobiological difference between volumetric modulated arc therapy (VMAT) and 3-dimensional conformal radiotherapy (3DCRT) in organ at risk (OAR) lumbosacral plexus (LSP) in cervical cancer patients.

**Materials and methods:** 30 patients of cervical cancer who were treated using 3DCRT or VMAT along with chemotherapy followed by brachytherapy were enrolled. LSP was delineated retrospectively. Dosimetric and radiobiological difference was evaluated. Patients were followed for radiation induced lumbosacral plexopathy (RILSP).

**Results:** Median follow-up was 12 months (3-16 months). 53.3% of patients were treated by 3DCRT and 46.7% by VMAT. The mean ( $\pm$ SD) LSP volume:  $119.03 \pm 15 \text{ cm}^3$ . The mean volume percentages (%) of the LSP: V5, V10, V20, V30, V40, V50, V55, and V60 were 100%, 99.8%, 99.2%, 94.3%, 84.03%, 59.7%, 0%, 0%, respectively. All patients received doses to the LSP in excess of 50 Gy, one patient received 55 Gy. A statistically significant difference was observed in the median value of V20, V30, V40, V50, D50, P2, P4, P7, P8, P9, and P10 across two different techniques of radiotherapy — VMAT and 3DCRT. None of the patients presented with RILSP. NTCP value was less in VMAT plans compared to 3DCRT, which is also statistically significant.

**Conclusion:** RILSP is a rare and often refractory complication of pelvic radiotherapy. Advance radiotherapy technique with proper OAR delineation and constraint can prevent the occurrence of RILSP. VMAT has potential benefits for the probability of dose reduction in LSP. Further studies are required focusing on dose distribution in LSP-OAR and radiotherapy modality.

**Key words:** lumbosacral plexuses; VMAT; 3DCRT

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## Introduction

Cervical cancer is the second most common cancer in India in women, accounting for 6-29% of all cancer cases [1]. Surgery and chemo-radiation are widely utilized treatments for cervical cancer.

In locally advanced cervical squamous cell carcinoma, concurrent chemo-radiotherapy (CCRT) is the standard of care. Radiotherapy (RT) technology has improved considerably, from conventional 2-dimensional four-field box technique to 3-dimensional conformal radiotherapy (3DCRT) tech-

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niques, which emerged as a preferred treatment for gynecologic malignancies since it gave better and more precise target coverage and significantly reduced the volume of radiation-exposed bladder and bowel. Further, the introduction of new radiotherapy techniques such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) in pelvic malignancies have significantly reduced radiation dose to normal organs at risk (OARs) in the vicinity of the target while allowing dose escalation to the tumor and regional lymph nodes. It has significantly decreased the incidence of gastrointestinal, urinary, and hematological toxicities [2]. However, dose to undelineated OARs is an area of concern. The accurate delineation of all OARs is critical to the success of conformal radiotherapy techniques for dose avoidance to adjacent normal structures.

Radiation-induced lumbosacral plexopathy (RILSP) in cervical cancers is a rare and late effect but extremely serious complication of pelvic irradiation. Lumbosacral plexus (LSP) is such an organ that is not routinely contoured for patients undergoing external beam radiotherapy (EBRT) for pelvic malignancies. This may lead to dose dumping, with higher than expected doses placed in the LSP because it is not specified as an OAR [3]. The incidence of RILSP ranges from 1.3% to 6.67%. LSP usually occurs as early as three months to several years after radiation completion and usually presents with symptoms such as paresthesias, numbness, dysesthesias, pain, lower extremity weakness and, rarely, urinary or fecal incontinence. Neurological symptoms are progressive and irreversible in behavior, hence, compromising the quality of life [4, 5]. Also, a majority of times, these complications are unnoticed or misdiagnosed by treating oncologists, resulting in under-reporting of RILSP incidence.

Therefore the study aims to evaluate dosimetric and radiobiological difference between VMAT and 3DCRT technique in OAR: LSP in cervical cancer patients treated with radiotherapy and concurrent chemotherapy.

## Materials and methods

### Patient selection

Retrospectively, 30 cervical cancer patients who were treated at our institute between November

2018 to December 2019 using 3DCRT or VMAT radiotherapy technique and concurrent chemotherapy followed by high dose rate brachytherapy (BT) were enrolled.

Inclusion criteria: histologically proven cervical cancer, FIGO stage IB3 to IIIC, no distant metastasis on imaging, no previous history of pelvic irradiation.

Exclusion criteria: presence of metastatic disease, recurrence/second primary, uncontrolled diabetes mellitus, adjuvant hysterectomy

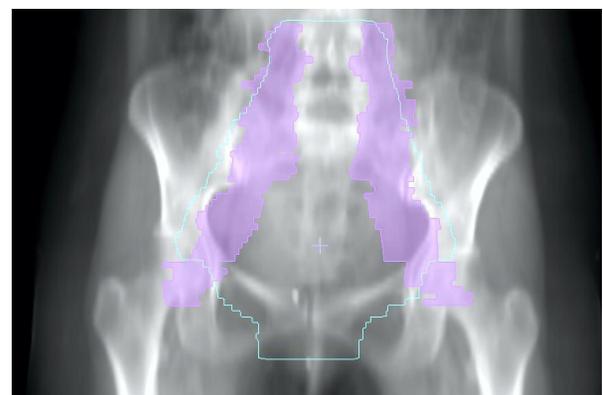
### Delineation of lumbosacral plexus (LSP)

LSP was delineated retrospectively on initial treatment plans with no dose limitations in every patient from the L4–L5 interspace to the level of the sciatic nerve using a 5-mm-diameter paint tool on the planning CT scan of 2.5 mm slice thickness by the radiation oncologist using the anatomic atlas developed by Yi et al. [6] (Fig. 1). The referenced structures included the psoas, iliacus, piriformis, obturator internus, and gluteus maximus muscles, the common and internal iliac arteries and veins, and relevant vertebral bodies and sacral bones.

### Treatment techniques

Treatment plans were generated for Elekta Versa HD with 160 agility MLCs (Elekta Oncology, UK) using the Monaco treatment planning system (v5.11.02, Elekta CMS, Sunnyvale, CA).

3DCRT plans were created using 6 and 10 MV photon beams. Four fields were shaped at the beam's eye view to encompass the PTV shape using MLC at gantry angles of 0°, 90°, 270° and 180° and calcu-



**Figure 1.** Right and left lumbosacral plexus (purple) on digitally reconstructed radiographs; PTV — planning target volume (cyane blue)

lated using Collapsed Cone(CC) dose calculation algorithm.

VMAT plans were created using dual arcs with a 6 MV photon beam. In the first step, the pencil beam algorithm was used for rapid modelling, and the final dose optimization was done with the Monte Carlo (MC v1.6) algorithm using a grid size of 0.3 cm, minimum segment width of 1 cm, medium level fluence smoothing and a calculation uncertainty of 1%.

### Analysis of the dose distribution

Based on each patient’s dose-volume histogram (DVH), the total LSP volume, mean dose (Dmean) LSP, maximum dose (Dmax) LSP, D 50%, D (0.03 cm<sup>3</sup>) and volume percentages of the LSP absorbing, respectively, 5, 10, 20, 30, 40, 50, 55, and 60 Gy (V5, V10, V20, V30, V40, V50, V55, V60) were then estimated. Also, point doses were calculated on LSP as P1 and P2 (point doses at the right and left portion of LSP at the level of the L4/L5 interspace), P3 and P4 (point doses at the right and left portion of LSP at the level of interspace L5/S1), P5 and P6 (point doses at the right and left portion of LSP at the level of the inferior part of the sacroiliac joint), P7 and P8 (point doses at the right and left portion of LSP at the level of ischial spine/acetabulum) and P9 and 10 (point doses at the right and left portion of LSP at the levels of the femoral neck.

### Normal tissue complication probability (NTCP) for LSP

The Lyman-Kutcher-Burman Normal Tissue Complication Probability (LKB-NTCP) model was used to determine lumbosacral plexopathy in this study. The following formulas express the LKB-NTCP model:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\alpha}^t \exp(-\frac{x^2}{2}) dx \quad (1)$$

$$t = \frac{D - TD_{50}}{m \cdot TD_{50}} \quad (2)$$

$$TD_{50}(v) = TD_{50}(1) \cdot v^{-n} \quad (3)$$

$$v = \frac{V}{V_{ref}} \quad (4)$$

Where D is the uniform dose calculated by the generalized equivalent uniform dose (gEUD)

formula proposed by Niemierko; TD50 is the tolerance dose for a 50% complication probability for uniform doses to the LSP; m is a dimensionless parameter to determine the slope of the complication probability according to dose curve; n is the parameter for the volume dependence of the complication probability and Vref is a reference volume.

The tolerance dose for 50% (TD50) complication, the values of n = 0.03, m = 0.12 and TD50 = 75 Gy were taken in this model for predicting complications of LSP [7]. All DVH data were exported from TPS and imported into MATLAB 2018a (Mathworks, Natick, MA, USA) to calculate NTCP.

Patients were followed every 3 months. At each follow-up visit, a detailed history was taken and a clinical examination was performed. Magnetic resonance imaging (MRI) pelvis was done if clinically indicated for recurrence or RILSP. The RILSP was defined as the occurrence of paresthesias, numbness, dysesthesias, pain, or lower extremity weakness. The time of onset of RILSP was defined as the interval between the end of concurrent chemoradiation and the occurrence of the first RILSP symptom.

### Statistical analysis

The data was entered into Microsoft excel sheet and exported into SPSS version 20. Descriptive measures were presented in tabular form with mean (±SD) for continuous variables (dosemetric properties of LSP, Age, tumor size) and proportion for discrete variables (clinic pathological and treatment characteristics). In addition, Dosimetric data, total LSP volume, LSP mean dose (Dmean), LSP maximum dose (Dmax), D50%, D0.03 cm<sup>3</sup>, V5, V10, V20, V30, V40, V50, V55, and V60, and point doses (P1, P2, P3, P4, P5, P6, P7, P8, P9, and P10) were compared between two different radiotherapy modalities (VMAT vs. 3DCRT) using Mann-Whitney U non-parametric test. A p-value lower than 0.05 was considered statistically significant.

### Results

A total of 30 patients were retrospectively analyzed. The demographic distribution and patient characteristics were summarized in Table 1. In current study, the majority of the patients presented with FIGO stage IIB (46.7%) followed by stage IIIC1 (40%) cervical cancer with a mean age of 53.8 years (± 8 years). Only 6% and 20% of patients had

**Table 1.** Clinic pathological and treatment characteristics

		n (%)
Age (mean ± SD)	53.8 (8)	
<b>Hypertension</b>		
Yes		2 (6.7%)
No		28 (93.3%)
<b>Diabetes</b>		
Yes		6 (20%)
No		24 (80%)
Tumor size (mean ± SD)	4.8 (0.761) [4–6 cm]	
<b>FIGO staging</b>		
IB3		1 (3.3%)
IIA2		1 (3.3%)
IIB		14 (46.7%)
IIIC1		12 (40%)
IIIC2		2 (6.7%)
<b>Nodal status</b>		
Unilateral		5 (16.7%)
Bilateral		9 (30%)
No lymph node		16 (53.3%)
<b>Radiotherapy technique</b>		
VMAT		14 (46.7%)
3DCRT		16 (53.3%)
Median follow-up (months)		12 [IQR:3 to 16]

SD — standard deviation; FIGO — International Federation of Gynecology and Obstetrics; VMAT — volumetric modulated arc therapy; 3DCRT — 3-dimensional conformal radiotherapy

a history of hypertension and diabetes, respectively. The m, 53.3% of patients, were treated using the 3DCRT technique, while 46.7% with the VMAT technique, to total prescribed doses covering 95% of the planned target volume, PTV (Fig. 2). All pa-

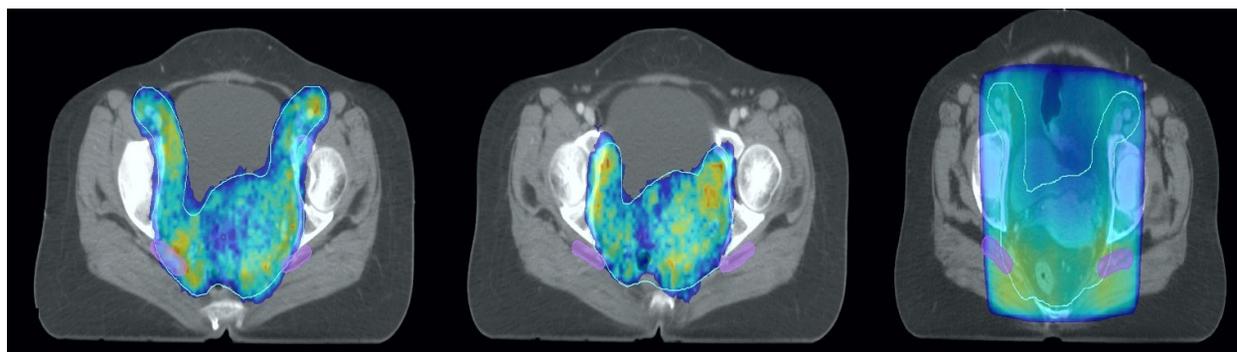
tients received 50 Gy in 25 fractions at 200 cGy per fraction, 5 days a week over 5 weeks, along with concurrent chemotherapy consisting of weekly cisplatin 40 mg/m<sup>2</sup> followed by image-guided high dose rate brachytherapy (HDR-BT), 21–22.5 Gy in 3 sessions. Median follow up was 12 months (range 3–16 months).

### LPS dosimetry analysis

In current study, the mean ± SD LSP volume was 119.03 ± 15 cm<sup>3</sup> (range, 92.22–150.65 cm<sup>3</sup>). The mean dose (Dmean) and mean maximal dose (Dmax) to the LSP were 47.1 Gy (range, 44–52 Gy) and 53.4 Gy (range, 52–55 Gy). The mean volume percentages (%) of the LSP absorbing, respectively, 5, 10, 20, 30, 40, 50, 55, and 60 Gy were then calculated (V5, V10, V20, V30, V40, V50, V55, and V60), at 100%, 99.8%, 99.2%, 94.3%, 84.03%, 59.7%, 0%, 0%, respectively. The dose received by 50% of the volume of the LSP (D50) was 50.4 ± 1 Gy (range: 48–52 Gy). While dose delivered to 0.03cm<sup>3</sup> (D 0.03 cc) volume was 52.6 ± 1 Gy (range: 50–55 Gy) (Tab. 2). All 30 patients received doses to the LSP in excess of 50 Gy, with one patient receiving a maximum of 55 Gy. No patients were found to have received > 55 Gy to the LSP. The cumulative LSP dose-volume histograms (DVHs) for all patients are shown in Figure 3. The points P3, P5, P6 and P7 absorbed the highest doses when compared with other points, median dose 50.9 Gy, 51.6 Gy, 51.2 Gy and 50.9 Gy, respectively.

### 3DCRT versus VMAT: impact on LSP dose distribution

Out of 30 patients, 16 patients were treated using the 3DCRT technique, and 14 patients were treat-



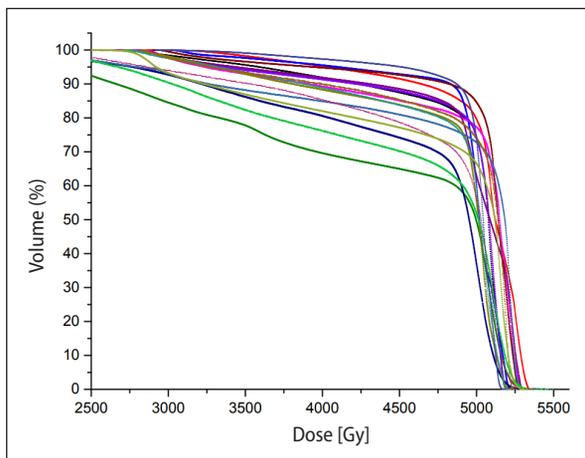
**Figure 2.** Dose coverage (95% isowash) of planning target volume [(PTV): cyane blue] for volumetric modulated arc therapy (VMAT) (A, B) and 3-dimensional conformal radiotherapy (3DCRT) (C) planning technique [lumbosacral plexus (LSP): purple]

**Table 2.** Dosemetric parameters of lumbosacral plexus (LSP)

	Mean ± SD	Range [Min-Maximum]
Volume LSP [cm <sup>3</sup> ]	119.03 ± 15	92.22–150.65
Dmean LSP [Gy]	47.1 ± 2	44–52
Dmax LSP	53.4 ± 1	52–55
V5 (%)	100	
V10 (%)	99.8 ± 1	97–100%
V20 (%)	99.2 ± 1	94–100%
V30 (%)	94.3 ± 5	80–100%
V40 (%)	84.03 ± 8	70–97%
V50 (%)	59.7 ± 12	37–85%
V55 (%)	0	
V60 (%)	0	
D50 [Gy]	50.4 ± 1	48–52%
D 0.03 cc [Gy]	52.6 ± 1	50–55%

SD — standard deviation

ed using the VMAT technique. In current study, the median dose to LSP (Dmean) by VMAT is 45 Gy lower than the 3DCRT technique which is 48.8 Gy ( $p < 0.001$ ). But maximal dose to LSP (Dmax) by VMAT was higher than the 3DCRT technique, 54.45 Gy and 52.54 Gy, respectively, which was statistically significant ( $p < 0.001$ ). The median volume percentages (%) of the LSP receiving 20, 30, 40 and 50 Gy (V20, V30, V40 and V50) were comparatively lower in VMAT (V20: 98.35%, V30: 91.59%, V40: 76.6% and V50: 50%) then 3DCRT technique



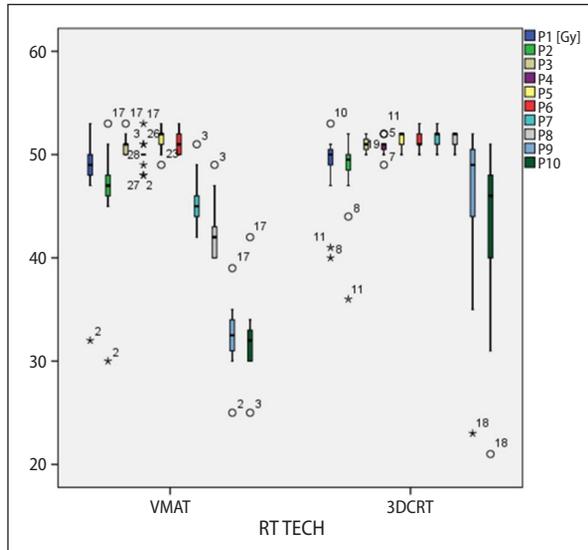
**Figure 3.** Cumulative lumbosacral plexus (LSP) dose-volume histograms (DVHs) for all patients

(V20: 100%, V30: 97.96%, V40: 90.66 and V50: 69.64 %) showing statistical significance. The median dose received by 50% of the volume of the LSP (D50) was lower in VMAT (50 Gy) compared to 3DCRT (50.8 Gy), showing statistical significance. Also, it was observed that median point dose to P1, P2, P4, P7, P8, P9 and P10 in VMAT were lower than 3DCRT, of which P2, P4, P7, P8, P9, P10 were found to be statistically significant (Tab. 3, Fig. 4).

Figure 5 shows relations between the NTCP values and analysed techniques. The NTCP values obtained for 3DCRT were significantly higher than the VMAT delivery technique ( $p < 0.001$ ). The me-

**Table 3.** Lumbosacral plexus (LSP) dosimetry and comparison between volumetric modulated arc therapy (VMAT) vs. 3-dimensional conformal radiotherapy (3DCRT)

	Median value across patients receiving VMAT	Median value across patients receiving 3DCRT	U-value	z-value	p-value
Dmean LSP [Gy]	45.00	48.88	219.5	4.524	0.000
Dmax LSP [Gy]	54.45	52.54	8.5	-4.453	0.000
V20 (%)	98.35	100.00	176.5	3.056	0.006
V30 (%)	91.59	97.96	208	4.043	0.000
V40 (%)	76.60	90.66	221.5	4.561	0.000
V50 (%)	50.00	69.64	210	4.085	0.000
D50 [Gy]	50.00	50.81	174.5	2.839	0.008
P2	47.22	49.38	164	2.181	0.031
P4	50.00	51.05	170.5	2.562	0.013
P7	45.00	51.65	220	4.576	0.000
P8	42.11	51.62	224	4.751	0.000
P9	32.30	48.82	207.5	3.979	0.000
P10	32.20	45.90	196.5	3.523	0.000



**Figure 4.** Box plot of point dose at different points in lumbosacral plexus (LSP): volumetric modulated arc therapy (VMAT) vs. 3-dimensional conformal radiotherapy (3DCRT)

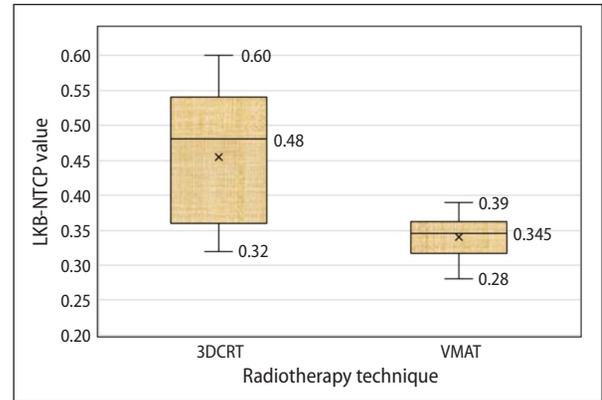
dian (IQR) of NTCP values for 3DCRT and VMAT were 0.48 (0.32 to 0.60) and 0.34 (0.28 to 0.39), respectively.

In present study, 3 out of 30 patients presented with complaints of per vaginal bleeding and unilateral pain at lower back and were confirmed as recurrence on clinical examination and on MRI at 3, 12 and 15 months of follow-up, respectively. One patient expired due to myocardial infarction 1 year post-treatment. However, no patient presented with RILSP symptoms or showed associated changes on MRI.

## Discussion

In Cervical cancer treated with concurrent chemo-radiotherapy, late gastrointestinal (GI), and/or gastro-urinary (GU) toxicity are common and remains a clinical concern and a dose-limiting factor. Late high-grade GI toxicity is reported in up to 35% of cervical cancer patients undergoing chemo-radiation [8]. Using conformal radiotherapy techniques/IMRT has reduced the incidence and severity of GI toxicity in patients with gynecological malignancies. But most missed late toxicity associated with pelvic irradiation is lumbosacral plexopathy.

RILSP is rare, with limited publications and studies to report, unlike radiation-induced brachial



**Figure 5.** Normal tissue complication probability (NTCP) comparison between volumetric modulated arc therapy (VMAT) vs. 3-dimensional conformal radiotherapy (3DCRT)

plexopathy, which is relatively common in patients irradiated for breast carcinoma. The incidence of RILSP is likely underreported because its symptoms are commonly overlooked by treating oncologists. Clinical manifestations of RILSP often include an initial presentation of painless weakness, which occurs bilaterally in up to 80% of patients, from months to many years after the completion of radiotherapy [9]. Only 10% of patients initially present with pain, but eventually it affects almost 50% of patients. Symptoms associated with RILSP are nonspecific, and it is important to distinguish RILSP from lumbosacral plexopathy due to other causes such as degenerative joint processes, diabetes-related, chemotherapy-induced, and plexopathy from recurrent tumor. In case of diseases spread or metastatic deposits associated with LSP, the pain may be relieved by either lying on one side with the knees flexed or flexing the affected extremity at the hip in bed. While in RILSP, pain is not relieved with positioning in patients [10]. Besides, neurological findings are unilateral in patients with diseases or metastatic deposits associated with LSP, and bilateral in RILSP [11]. Autonomic involvement or sphincter disturbance is unusual in patients with RILSP [12].

As per literature, tolerance to the spinal cord and cauda equina (TD 5/5: tolerance dose; 5% probability of severe sequelae in 5 years), from which the LSP arises, has been estimated at 47 Gy and 60 Gy, respectively, for full-volume irradiation [13]. However, the radiosensitivity of peripheral nerves is likely enhanced by concomitant chemotherapy, and the RILSP has been reported at much

lower doses (50–60 Gy) [14]. With radiotherapy doses typically reaching > 50 Gy with concomitant chemotherapy in the treatment of gynecologic and other pelvic cancers, it is important to consider this late sequel during treatment planning. Although the exact mechanism is not clear, it is thought to be associated with localized ischemia and subsequent soft-tissue fibrosis caused by microvascular insufficiency [15].

In the current study, LSP volume was observed to be 92.22–150.65 cm<sup>3</sup> (mean ± SD: 119.03 ± 15 cm<sup>3</sup>), which was larger than those described by Yi et al. [6] and Min et al. [16], LSP volume: 71–138 cm<sup>3</sup> and 40.9–58.4 cm<sup>3</sup>, respectively. The reason for larger volumes can be explained by the contouring of lumbosacral plexuses regions (LSPRs) as proposed by Min et al. [16], when LSP was radiologically invisible in the present series. The mean maximal dose to LSP was 53.4 Gy in the present study. This finding was comparable with Yi et al. [6], Min et al. [16], and Chaudhary et al. [17] studies, observed mean Dmax LSP: 52.6 Gy, 52.2 Gy, and 55.67 Gy, respectively. Further, in the present study, mean volume percentages (%) of the LSP absorbing 30 Gy, 40 Gy and 50 Gy were calculated at 94.3%, 84.03% and 59.7%, respectively. This was comparatively higher than that reported in studies by Yi et al. [6] (V30: 73.2%, V40: 58%, V50: 22%), Chaudhary et al. [17] (V30: 84.6%, V40: 78.16%, V50: 55.04%) and Tunio et al. [18] (V30: 75.1%, V40: 52.8%, V50: 27.7%) (Tab. 4). This variation might be due to different radiotherapy techniques, concurrent chemotherapy regimens, and higher point doses to P3, P5, P6 and P7. In present study, 53.3% of patients were irradiated with 3DCRT while only 46.7% of patients were treated with VMAT technique in contrast to Yi et al. [6] and Tunio et al. [18] study, where all patients had undergone pelvic irradiation using intensity-modulated radiotherapy (IMRT) technique. Min et al. [16] in his study showed that the mean percentage of the LSP receiving 40 Gy (V40 Gy) and 50 Gy (V50) was lower in IMRT (V40: 61.3%, V50: 38.8%) compared to conventional (V40: 54.4%, V50: 55.3%) modality. This observation was similar to the present study, which showed a significant reduction in V40 and V50 values for VMAT when compared to the 3DCRT technique (p < 0.01). Tunio et al. [18] concluded that IMRT planning, especially focusing on the levels of P5, P6, P7, and P8 can significantly reduce the risk

**Table 4.** Literature review of dosemetric data of lumbosacral plexus (LSP)

Study	N	Prescribed dose EBRT (dose/fraction)	Median Follow-up in months (range)	Malignancy	LSP volume [cm <sup>3</sup> ]	Mean Dmax LSP [Gy]	V30 (%)	V40 (%)	V50 %	V55 %	Incidence of RILSP (onset after treatment)
Yi et al. [6]	15	50.4–59.4 Gy (1.8 Gy)	(1–33)	Rectal and anal cancer	100 (71–138)	52.6	73.2 (32–94)	58 (24–77)	22 (0–71)	0.5 (0–3)	7% (13 months)
Min et al. [15]	10	50.4–66 Gy (1.8–2 Gy)	5.2 (0.9–10.4)	Cervica, endometrial, rectal and anal cancer	40.9–58.4	52.2	–	57.83 (30–74.5)	16.86 (0–55.3)	1.23 (0–11.2)	None
Tunio et al. [17]	50	50.4–59 Gy (1.8 Gy)	60 (24.1–65.4)	Cervical cancer	93.2 (72.3–117.3)	56.7	77.2 (64.3–91.6)	61.8 (55–64.3)	44.4 (36–53)	8 (6.1–10.2)	8% (at 20, 43, 52, 52 months, respectively)
Chaudhary et al. [16]	15	50.4–66.6 Gy (1.8–2 Gy)	–	Rectal cancer	59.84 (33–77.7)	55.67	84.6 (70.7–95)	78.16	55.04	0	None (no follow-up done)
Present study	20	50 Gy (2 Gy)	12 (3–16)	Cervical cancer	119.03 (92.2–150.65)	53.4	94.3 (80–100)	84.03 (70–97)	59.7 (37–85)	0	None (follow-up done upto 16 months)

EBRT — external beam radiotherapy; RILSP — radiation induced lumbosacral plexopathy

for RILSP. In current study, statistical difference in dose level at P2, P4, P7, P8, P9 and P10 was observed due to the radiotherapy planning technique. Using IMRT reduces radiation dose to normal organs at risk (OARs) in the target's vicinity while allowing higher doses to the tumor and regional lymph nodes. Prior studies have demonstrated reduced dose and toxicity to surrounding normal structures for the treatment of cervical [19], rectal [20] and anal cancers [21] when using IMRT. Also, delivery of IMRT in a single gantry arc as VMAT, is an efficient dose delivery technique with comparable dose distribution to standard IMRT [22]. Moreover, thinner leaf width multileaf collimators (MLC) may result in better planning target volume (PTV) coverage and higher target conformity [23]. Therefore, accurate delineation of all OARs is critical to the success of IMRT/VMAT for dose avoidance to adjacent normal structures.

Also, the difference in total dose and dose per fraction as per cancer site may impact LSP dosimetric parameters. The current study focused only on patients diagnosed with advanced stage cervical cancer, treated with external beam radiotherapy (EBRT) to a dose of 50 Gy in 25 fractions at 200 cGy per fraction followed by HDR brachytherapy (BT) delivered to dose 21–22.5 Gy in 3 sessions, one week apart. Tunio et al. [18], similar to the present study focused on cervical cancers, treated with total doses ranging between 50.4 to 59.0 Gy (median, 54 Gy) in 1.8 Gy per fraction, followed by BT 21 Gy in three sessions (Tab. 4).

RILSP usually occurs as early as 3 months to several years after completion of radiation though the median symptom-free interval has been reported at 5 years [9]. In the present study, median follow-up was 12 months (range 3–16 months). During this period none of the patients presented or was diagnosed with RILSP. These findings were comparable with Yin et al. [6] and Tunio M et al. [18] studies. Yin et al. observed that one patient (7%) out of 15 was found to have developed RILSP at 13 months after treatment [6]. Whereas, Tunio M et al. observed that 4 patients (8%) out of 50 were found to have grade 2/3 RILSP at 20, 43, 52 and 52 months, respectively (median follow up: 60 months, range:24.1–65.4 months) [18] (Tab. 4).

Therefore, the possible explanation for none of the patients presented with RILSP in the present study would be limited follow-up time. Thus, with

longer follow-up, more patients may eventually develop RILSP, given its tendency for late occurrence. Also, including other pelvic malignancies, like uterine, rectal, anal and prostate cancer may provide us with a large sample size and adequate data for analyzing dosimetric parameters that may increase the risk for RILSP and further strengthen the data and their association with this late disabling toxicity.

Moreover, the management of RILSP is cumbersome and often refractory, thus highlighting the need for prevention. Treatment goals include adequate pain control and preservation of the remaining neurologic function. Physical therapy, assistance devices for ambulation, and pain management with oral narcotics and local peripheral nerve blocking agents are often used. Other pharmacologic agents that may be helpful include anticoagulants, antiepileptics, tricyclic antidepressants, and corticosteroids. Hyperbaric oxygen has also been reported to improve symptoms of radiation-induced plexopathy [24]. Therefore, future studies will be needed to spread awareness regarding RILSP to prevent under- or misdiagnosis of this debilitating, permanent, and often refractory complication of pelvic radiotherapy amongst treating oncologists and better define parameters to reduce the occurrence of RILSP.

## Conclusion

RILSP is rare, but unpleasant late toxicity associated with pelvic radiotherapy in cervical cancer and other pelvic malignancies. In the present study, all patients received doses to the LSP in excess of 50 Gy, with one patient receiving a maximum of 55 Gy (a maximum dose of 50 Gy to LSP was received by most of the patients, except one who received 55Gy). Also, a statistically significant difference was observed in the median value of V20, V30, V40, V50, D50, P2, P4, P7, P8, P9, and P10 across two different techniques of radiotherapy — VMAT and 3DCRT. In the current analysis the obtained NTCP value was less in VMAT plans compared to 3DCRT, which is also statistically significant. So, our study shows that the VMAT has potential benefits for the probability of dose reduction in LSP. However, none of the patients presented with RILSP in the present study. LSP delineation is not yet performed routinely, probably because

of limited literature data resulting in dose dumping and hot spots to undefined and unconstrained regions near the treated volumes, potentially leading to excessive doses to the LSP. Although improvised advanced radiotherapy techniques such as IMRT/VMAT with a proper target volume, OAR delineation and proper constraints to LSPs at the time of inverse planning can further prevent the occurrence of RILSP. Further large prospective studies are required in pelvic malignancies focusing on dose distribution in LSP–OAR with a longer follow-up period to assess the outcomes and improve quality of life post pelvic irradiation.

### Conflict of interests

None declared.

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