External Validation of the Lumbosacral Plexus Contouring Protocol Developed by Yi et al. (IJROBP 2012; 84:376-382) for Pelvic Malignancies

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Running head: External Validation of the Lumbosacral Plexus Contouring Protocol

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Abstract

Purpose: To evaluate interobserver variability in contouring lumbosacral plexuses (LSP) using the protocol developed by Yi *et al.* (IJROBP 2012; 84:376-382) and to review LSP dosimetries for conventional radiotherapy and intensity-modulated radiotherapy (IMRT) for pelvic cancers.

Methods and materials: Using the above-mentioned protocol, seven outliners independently contoured LSPs of 10 consecutive patients (5 patients treated with conventional radiotherapy and 5 with IMRT). Interobserver variability was reviewed visually by using planning axial computed-tomograph images and antero-posterior-digitally-reconstructed-radiographs (AP-DRRs). Dosimetries of LSPs were also calculated and compared.

Results: There was a notable learning curve for each outliner (duration to outline the first patient 45-185 minutes), versus 15-50 minutes after 6 patients. We found significant interobserver variability among outliners below the level of S2 nerve roots. The LSP volumes (mean volume range of 40.9 – 58.4 cc) were smaller than those described in the atlas paper (71 – 138 cc). The mean values of mean dose, maximum dose, V40Gy, V50Gy and V55Gy for patients treated with conventional radiotherapy and IMRT were 35.5Gy vs 33.6Gy, 52.2Gy vs 52.2Gy, 61.3% vs 54.4%, 14.9% vs 18.8% and 0% vs 2.5% respectively.

Conclusion: We conclude that the protocol developed by Yi *et al.* is a useful set of guidelines but suggest that additional at-risk components of the LSP also be contoured. We recommend that radiation oncologists practise “nerve sparing” radiotherapy by contouring LSPs especially when using IMRT. We propose the term “lumbosacral-plexus-regions (LSPR)” to highlight the fact that LSPs are not always radiologically visible structures but regions where they are likely to be present.

Key words: lumbosacral plexus, radiation-induced lumbosacral plexopathy, IMRT, pelvic cancer, lumbosacral plexus contouring protocol

Introduction

It is essential for treating oncologists to have a profound knowledge of tumoricidal doses and tolerance doses of various normal tissues to achieve loco-regional control of cancers with minimal or acceptable complications¹. Although the literature discussing incidences and grades of radiation-induced brachial plexopathy (RIBP) in patients treated with radiotherapy for head and neck, breast and lung cancers is abundant, Yi *et al.* noted in a recent paper that radiation-induced lumbosacral plexopathy (RILSP) has been under-recognised and under-reported². Patients with RILSP can present with insidious onset of pain, numbness or debilitating weakness and the latent period has been reported to vary from 1 month to 47.5 years³⁻⁹. Hence, symptoms of RILSP may not be observed if follow up is not long enough for this complication to develop. In addition, lumbosacral plexuses are not defined as an organ at risk in clinical trials, including those using IMRT, and RILSP is not routinely reported. Due to these reasons, the actual incidence of RILSP is not known.

In breast cancer patients treated with radiotherapy to supraclavicular regions, the median interval to onset of RIBP was reported to be 1-4 yrs with annual incidences of 0.2 - 0.4%, 1.8% and 2.9% when treated with EQD2 (Equivalent Dose in 2Gy per fraction) of 51.3Gy, 58.1Gy and 59.8Gy respectively^{10,11}. It was also reported that the risk of developing RIBP remained constant for a long duration with the percentage freedom from RIBP being 96.1%, 75.5%, 72.1% and 46% after 5, 10, 15 and 19 years respectively¹¹. It should be noted that breast cancer patients are treated with radiotherapy alone or with sequential chemotherapy while patients with pelvic cancers are often treated with concurrent chemoradiotherapy using equivalent or higher doses of radiation. Moreover, the increased risk of neuropathy from adding radiosensitising agents, especially neurotoxic platinum analogues, is poorly quantified. One further plausible contributing factor to the under-reporting of RILSP is that neurological symptoms may instead be ascribed to Cisplatin chemotherapy.

Since the survival rates of patients with pelvic cancers such as gastro-intestinal or gynaecological malignancies have been improving over the last few decades especially when using chemo-radiotherapy with or without surgery, we believe that it is important to start practising “nerve sparing” radiotherapy by monitoring the dose to lumbosacral plexuses (LSPs) and assessing late onset neurological symptoms. This is especially pertinent for intensity-modulated radiotherapy (IMRT) where failure to outline the LSP as an organ at risk (OAR) may result in unwanted “dose dumping”.

Yi *et al.* developed a standardised guideline to contour LSPs which we believe is essential in the era of precision radiotherapy². As the use of IMRT in pelvic malignancies in our department increased, we decided to either adopt or develop a protocol to contour LSPs when using IMRT. The aim of our study is to evaluate interobserver variability in contouring the LSPs using the Yi *et al.* protocol. We also reviewed dosimetries of LSPs in patients treated with conventional radiotherapy techniques and IMRT for their pelvic cancers.

Materials and methods

Using the instructions described in the above-mentioned paper, LSPs of ten consecutive patients treated with radiotherapy for pelvic cancers (gastrointestinal or gynaecological) at the Alan Walker Cancer Centre were contoured by four radiation oncologists, one radiation oncology advanced trainee and two senior radiation therapists. Five patients were treated with conventional 3-4 field techniques and another five with multi-field IMRT where LSPs were not used as an organ at risk (OAR) during radiotherapy planning and dose optimisation.

All ten patients were de-identified and imported to the Pinnacle (version 9.2, Philips, Fitchburg, WI, USA) contouring system. Strict instructions were given to all seven outliners to contour LSPs independently in a blinded fashion. Duration and comments were recorded in a standardised form created for this project. None of the outliners involved in this study have previously contoured LSP with or without any guidelines.

Interobserver variability was reviewed visually by using planning CT axial images and digitally-reconstructed-radiographs (DRRs) (Figs 1 and 2). A quantitative analysis of all the volumes across all outliners was also performed (Table 2). Dosimetries of LSPs were also calculated and compared between the two groups (conventional multi-field and IMRT).

Results

Patient, disease, and treatment details are shown in Table 1. There were six ano-rectal and four gynaecological cancers. Prescribed doses ranged from 50.4 to 66 Gy at 1.8-2.0 Gy per fraction, and 6 patients had synchronous chemotherapy.

We found that there was a very significant learning curve with a mean outlining duration of 91 minutes (range 45 -185 minutes) for Patient 1, gradually falling to 24 minutes (15-30) for Patient 10 (Table 1). Corresponding outlining durations for radiation therapists vs clinicians were 162-185 vs 45-75 minutes for Patient 1 and 30 vs 15 - 30 minutes for Patient 10, respectively. Patients 3 to 5 were simulated in prone position resulting in a blip (secondary learning curve) at Patient 3.

The AP-DRR of the LSPs of Patient 10 contoured by clinicians, radiation therapists and all outliners are shown in Figs. 1 (A-C). There was notable interobserver variability at all levels, particularly below the sacral nerve root two (S2) level. The LSP volumes in our study were found to be significantly smaller (mean range 40.9 - 58.4 cc) than those described in Yi *et al.* paper (71 - 138 cc).

Table 2 summarises the dosimetric analysis of LSPs outlined by all investigators. The average mean doses and maximal doses for the conventional and IMRT patients were comparable (35.5Gy vs 33.6Gy; 52.2Gy vs 52.2Gy and 61.3Gy vs 54.4Gy, respectively) but the mean percentage of LSP receiving 40Gy or greater (V40Gy) appeared to be slightly lower in IMRT patients (61.3% vs 54.4%, respectively). The mean percentage of V50Gy for the three IMRT patients prescribed 45Gy to 54Gy was found to be 0% in each case while it was 7.5 - 28.3% for the five conventional cases prescribed 50.4 to 54Gy. On the other hand,

for the two IMRT patients prescribed 59.4 and 66 Gy, mean V50Gy was 55.3% and 38.8%, although mean V55Gy was only 1.1% and 11.2% respectively. No LSP in this cohort received ≥ 60 Gy (V60Gy = 0% for all patients). The IMRT figures could, of course, have been improved if constraints for LSPs had been set at the time of inverse planning.

At the time of writing, no lumbosacral plexopathies had been detected but five patients were lost to follow-up: three from remote regional areas did not attend follow-up appointments; one moved interstate; and the fifth died prior to her first follow-up visit (the cause of death not related to radiotherapy or malignancy) (Table 1). The median duration of follow-up for the remaining five patients was 5.2 months (range 0.9 to 10.4 months).

Discussion

In the modern era, a high level of precision can be achieved by creating 3D target volumes and OARs on a high-quality planning system. Highly conformal dose distribution and increased normal tissue sparing are well known advantages of inverse planning IMRT but dose conformity and OAR toxicity cannot be optimised if dose constraints to OARs are not set in the first place. Consistent guidelines to contour OARs, specification of dose constraints and scoring systems are required to monitor dose levels, to document toxicities and to implement appropriate management plans in order that cancer survivors experience minimal side effects.

Although infrequent, radiation-induced peripheral nerve plexopathies result in debilitating pain, progressive weakness, numbness or loss of reflexes^{10,12} but effective treatments are lacking. Developing an effective protocol to outline an organ at risk is the first critical step in the dose monitoring process. We congratulate Yi *et al.* in developing a standardised LSP protocol and have performed an independent external validation of their protocol which we believe is an important quality assurance second step.

The notable inter-observer variability at all levels reflects inherent difficulties in transferring information from a limited set of 2-D axial slices from a single patient on to planning CTs of patients with varying body habitus and treatment positions. However, immediately below the S2 level where there is a sudden transition from sacro-iliac joint to “free” pelvic bones, the variability was more pronounced. This was probably due to the fact that there was no written instruction or illustrated axial CT image in the atlas to guide outlining in that region (Figs. 1 and 2). A composite AP-DRR would also have been helpful to guide outliners when reviewing their final volumes. We provide a DRR for this purpose (Fig. 4B). The smaller volumes of LSPs in our study compared to those described in the Yi *et al.* paper may be due to differing interpretation of outlining instructions. Our outliners might have been less generous but it is difficult to tell in the absence of an AP-DRR in the atlas paper. We did not find the prone position to be problematical with respect to the outlining protocol (apart from a secondary learning curve). It should be noted that the resulting LSP volumes seen in the AP-DRR are “non-anatomical” as nerves do not in reality exit horizontally and then turn down at right angles.

As the lower pre-lumbar and pre-sacral regions (with margin) are generally included when treating pelvic malignancies, the components of nerve roots within the spinal canal (cauda equina) are at a similar risk from radiation as the more distal (extra-vertebral) components.

This is conceptually different from the brachial plexus situation where the nerve roots essentially emerge directly from the cord, a site which is already routinely strictly dose limited, unlike the lumbosacral part of the spine. We believe that these more proximal components of the nerves should also be included when outlining LSPs. Therefore, we propose an interim modified version of the LSP contouring protocol developed by Yi *et al.*, CT slices for which are shown in Fig. 3.

Although LSPs are relatively fixed structures inside the pelvis, until or unless MRI (which can show nerves clearly) is routinely incorporated into the planning process, LSPs cannot be outlined with confidence. Therefore, we propose the term “lumbosacral-plexus-regions (LSPR)” to indicate where lumbosacral plexuses are likely to be present (as distinct from structures radiologically visible on CT such as parotid, spinal cord, etc). Since the main objective of contouring LSPRs is to limit dose dumping to these regions during inverse planning IMRT, LSPRs may need to be outlined more generously than other structures due to this uncertainty in their location.

A number of modern radiotherapy departments including ours require more radiation therapist input in outlining OAR (which should be checked by the treating radiation oncologist at the time of plan approval). We therefore invited two of our senior radiation therapists who were keen to outline LSPs and participate in our project. Although the learning curve for them was found to be steeper than that of clinicians, they eventually took a similar amount of time for the later patients and their volumes were found to be satisfactory when reviewed by radiation oncologists. Our peripheral center has only one permanent radiation oncologist but an adequate radiation therapist workforce. In centers like ours, we believe that radiation therapists should be permitted to outline certain OARs if they are provided with training and a comprehensive set of guidelines.

Heron *et al.* reviewed patients with gynaecological malignancies treated with radiotherapy and reported that one of the advantages of IMRT over conventional 3D radiotherapy was a significant reduction in treatment volumes for bladder, rectum and small bowel when using IMRT which could translate into possible reduction into potential acute and late radiation toxicities of these organs¹³. To our knowledge, no study to date has reported dosimetries of LSPs treated with either conventional radiotherapy or IMRT and incidences of RILSP in pelvic patients are not reported in large series. Although there are some possible effective treatment options for bowel and bladder toxicities (eg. medications, surgical management, argon plasma coagulation, hyperbaric oxygen therapy, etc.), we are aware of no effective treatment option for neuropathies.

Some earlier studies reported RILSP in patients treated with radiation doses of 30 – 62.25 Gy with a latency of 6 months to 12 years^{4,8}. However, in patients with risk factors such as concurrent chemotherapy, comorbidities (eg. diabetes, B12 deficiency) and higher radiation doses (eg. brachytherapy boost), RILSP was found to develop earlier than previously thought with latent periods ranging from 1 month to 26 months^{2,3,5,6}. Coulombe *et al.* and Georgiou *et al.* reported calculated doses to LSPs in patients with RILSP: less than 37Gy in 25 fractions in two patients treated with concurrent Cisplatin; and in the order of 73 Gy in four patients treated with pelvic radiotherapy followed by brachytherapy boost, respectively^{6,3}. A more detailed dosimetric analysis of a patient treated with concurrent 5-Fluorouracil and Mitomycin was reported by Yi *et al.*: mean dose 41.8Gy, V40Gy 68%, V50Gy 5% and V55Gy 1%². Another uncertainty is whether patients with RILSP in these

case reports have received higher prescribed doses and/or higher point doses than those without RILSP, except in the study by Yi *et al.*

Historically, the incidence and survival rate of early breast cancer treated with radical radiotherapy were higher than those of pelvic malignancies treated with radical radiotherapy with or without concurrent chemotherapy. Therefore, RIBP was more likely to be recognised and reported than RILSP. However, as the survival rate of pelvic malignancies has been improving over recent years, more cases of RILSP are likely to be reported.

We believe that LSPR should be included in clinical trials and departmental protocols. Structures such as LSPRs are not intended to be dose limiting OARs but instead, regions in which to avoid dose dumping or unacceptable hot spots. Emami *et al* reported TD (Tolerance Dose) 5/5 of spinal cord and corda equina to be 47Gy and 60Gy respectively. Therefore, it would be reasonable to keep below 47Gy (in 2 Gy per fractions) wherever possible, especially when using chemotherapy, and to aim for a maximum dose $\leq 60\text{Gy}$, until further data is available. Therefore, we recommend that radiation oncologists consider practising “nerve sparing” radiotherapy for patients treated with pelvic radiotherapy especially when using IMRT, and using this atlas as a guide. The logical next step would be to assess neurological symptoms on follow up visits and report them accordingly.

Our study has several limitations. The data set was limited to only 10 patients and since outlining duration still appeared to be declining, it is likely that, with further practice, even less time would be taken. The number of outliers was only seven, including two radiation therapists. The interobserver variability would presumably decline after a collaborative feedback meeting but this had not been undertaken at the time of writing. Since prescribed doses were not uniform, we cannot conclude whether dose to the lumbosacral plexus is higher by using either conventional or IMRT technique. Although no patient was reported to have developed RILSP in this cohort, the duration of follow-up was short and five patients were lost to follow-up.

Conclusion

We conclude that the LSP contouring atlas developed by Yi *et al.* is a very useful set of guidelines to contour LSP but propose some improvements based on our experience. Although the exact incidence of RILSP is not known, rather than waiting until more cases arise, we recommend that radiation oncologists practise “nerve sparing” radiotherapy by contouring LSPs especially when using IMRT and also to consider using this atlas as a guide. We propose the term “lumbosacral-plexus-regions” to highlight the fact that LSP are not visible on CT, but instead regions where they are likely to be present. They should be contoured generously if in doubt. Based on this principle, we also propose an interim modified version of the LSP protocol developed by Yi *et al.*

Conflict of interest statement

This study was performed without any external or internal funding and there was no conflict of interest.

Ethics approval

This study was approved by the local ethics committee.

For Peer Review

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Figure legends

Figure 1 AP DRR of LSP volumes contoured by clinicians (A), radiation therapists (B) and all outliners (C).

Figure 2 Axial images of all LSPs contoured by 7 outliners, from L4/5 nerve root level to the level of femoral neck. (A) L 4 nerve root level (B) L5 vertebral body level (C) L5 nerve root level (D) S1 vertebra level (E) S1 nerve root level (F) S2 nerve root level (G) S3 vertebra level (H) S3 nerve root level (I) S4/5 vertebrae level (J) Coccygeal level/upper femoral neck level

Figure 3. Our proposed interim volumes of the lumbosacral-plexus-region (LSPR) (A) L4 nerve root level (B) L5 vertebra level (C) L5 nerve root level (D) S1 vertebra level (E) S1 nerve root level (F) S2 nerve root level (G) S3 nerve root level (H) S4 nerve root level

Figure 4. AP DRRs of LSP volumes. (A) the proposed LSP volume (B) a representative LSP volume using the atlas

Table 1. Patient, tumour and treatment details.

	Age	Sex	Site	Stage	Radiotherapy technique	Total dose in Gray / dose per fraction per day / total number of fractions	Concurrent chemotherapy	Treatment position	Time from completion to last follow-up (months)
1	34	F	Cervix	T1bN0M0	Conventional 4 fields	50.4Gy / 1.8 / 28	Cisplatin	Supine	7.6
2	64	F	Endometrium	T2N0M0	Conventional 4 fields	54Gy / 1.8 / 30	Nil	Supine	10.4
3	27	M	Rectum	T2N2bM0	Conventional 4 fields	50.4Gy / 1.8 / 28	5-Fluorouracil	Prone	Lost to follow-up
4	18	F	Rectum	T3N0M0	Conventional 3 fields (45Gy) followed by 5 fields boost (5.4Gy)	50.4Gy / 1.8 / 28	5-Fluorouracil	Prone	Lost to follow-up
5	62	M	Rectum	T3N1bM0	Conventional 3 fields	50.4Gy / 1.8 / 28	5-Fluorouracil	Prone	0.9
6	59	F	Cervix	T2bN1M0	IMRT	59.4Gy / 1.8 / 33	Cisplatin	Supine	Lost to follow-up
7	64	M	Anal canal	T2N0M0	IMRT	54Gy / 1.8 / 30	Mitomycin + 5-Fluorouracil	Supine	5.2
8	70	F	Anal canal	T1N0M0	IMRT	66Gy / 2 / 33	Nil	Supine	3.4
9	82	F	Anal canal	T2N0M0	IMRT	50.4Gy / 1.8 / 28	Nil	Supine	Lost to follow-up
10	83	F	Endometrium	T2N0M0	IMRT	45Gy / 1.8 / 25 (followed by HDR boost)	Nil	Supine	Deceased prior to 1 st follow-up visit

Abbreviation: IMRT = intensity-modulated radiation therapy; HDR = High dose rate brachytherapy.

Table 2. Dosimetric and volume analysis of LSPs outlined by all participants in both conventional and IMRT groups

	Conventional radiotherapy							IMRT		
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Prescribed total dose	50.4Gy	54Gy	50.4Gy	50.4Gy	50.4Gy	59.4Gy	54Gy	66Gy	50.4Gy	45Gy
Mean outlining duration (minutes) (Range)	91 (45-185)	53 (20-120)	62 (40-125)	37 (15-60)	38 (20-75)	36 (20-75)	32 (15-50)	32 (20-50)	27 (15-40)	24 (15-30)
Mean volume (cc) (Range)	46.7 (30.5-66.8)	58.4 (38.5-95.7)	51.8 (31.2-95.4)	40.9 (33.8-60.2)	57.6 (40.1-88)	44.4 (25.4-69.8)	53.6 (33.6-74.3)	44.9 (27.2-67.4)	41.1 (25.6-53)	48.7 (30.6-64.6)
Mean (average) mean dose (Gy)	38.6	28.1	39.1	37.4	34.4	43.6	20.9	33.6	31.2	38.7
Mean (average) maximal dose (Gy)	52.5	54.0	52.0	51.2	51.4	56.2	49.4	59.4	48.5	47.5
Mean V40Gy (%)	66.6	55.6	64.0	63.7	56.6	74.5	30.1	52.6	52.4	62.2
Mean V50Gy (%)	7.5	21.7	28.3	8.9	8.1	55.3	0.0	38.8	0.0	0.0
Mean V55Gy (%)	0.0	0.0	0.0	0.0	0.0	1.1	0.0	11.2	0.0	0.0
Mean V60Gy (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Abbreviation: IMRT = intensity-modulated radiation therapy; LSP = lumbosacral plexus; VxGy (%) = percentage volume of LSP receiving xGy or greater.

122x324mm (122 x 122 DPI)

145x303mm (150 x 150 DPI)

147x285mm (150 x 150 DPI)

151x270mm (100 x 100 DPI)