Perineural spread of pelvic malignancies to the lumbosacral plexus and beyond: clinical and imaging patterns

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OBJECT Perineural spread along pelvic autonomic nerves has emerged as a logical, anatomical explanation for selected cases of neoplastic lumbosacral plexopathy (LSP) in patients with prostate, bladder, rectal, and cervical cancer. The authors wondered whether common radiological and clinical patterns shared by various types of pelvic cancer exist.

METHODS The authors retrospectively reviewed their institutional series of 17 cases concluded as perineural tumor spread. All available history, physical examination, electrodiagnostic studies, biopsy data and imaging studies, evidence of other metastatic disease, and follow-up were recorded in detail. The series was divided into 2 groups: cases with neoplastic lumbosacral plexopathy confirmed by biopsy (Group A) and cases included based on imaging characteristics despite the lack of biopsy or negative biopsy results (Group B).

RESULTS Group A comprised 10 patients (mean age 69 years); 9 patients were symptomatic and 1 was asymptomatic. The L5–S1 spinal nerves and sciatic nerve were most frequently involved. Three patients had intradural extension. Seven patients were alive at last follow-up. Group B consisted of 7 patients (mean age 64 years); 4 patients were symptomatic, 2 were asymptomatic, and 1 had only imaging available. The L5–S1 spinal nerves and the sciatic nerve were most frequently involved. No patients had intradural extension. Four patients were alive at last follow-up.

CONCLUSIONS The authors provide a unifying theory to explain lumbosacral plexopathy in select cases of various pelvic neoplasms. The tumor cells can use splanchnic nerves as conduits and spread from the end organ to the lumbosacral plexus. Tumor can continue to spread along osseous and muscle nerve branches, resulting in muscle and bone “metastases.” Radiological studies show a reproducible, although nonspecific pattern, and the same applies to clinical presentation.

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KEY WORDS perineural spread; pelvic cancer; perineural invasion; lumbosacral plexopathy; imaging

It is predicted that 453,360 new cases of pelvic malignancy (anorectal, genital, bladder, and ureteral cancer) will be diagnosed in the US in 2015.⁶³ Lumbosacral plexopathy (LSP) occurs in 0.71% of all cancer patients;³⁰ however, in the subgroup of pelvic cancer, it will be presumably higher.

Perineural spread of tumor from the organ to the lumbosacral plexus along the pelvic autonomic nerves has emerged as an alternate, logical explanation for select cases of neoplastic lumbosacral plexopathy (nLSP) in patients without extensive pelvic disease. This mechanism has been put forth for prostate,^{9,17,27,37} bladder,¹ rectal,¹⁸ and

cervical cancer.²⁸ We reviewed our institutional series of cases concluded as perineural spread of pelvic malignancy in search of clinical and radiological patterns.

Methods

After securing an approval from the institutional review board, we retrospectively reviewed our series of perineural spread of pelvic cancer. These were defined as cases of nLSP without extensive pelvic disease that demonstrated radiological signs of perineural tumor spread. These imaging signs were defined as enlarged lumbosacral plexus,

ABBREVIATIONS BNB = blood-nerve barrier; LSP = lumbosacral plexopathy; nLSP = neoplastic LSP; PNI = perineural invasion.

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spinal nerves or branching nerves (such as the sciatic nerves) on T1-weighted sequences that were hyperintense on T2-weighted sequences and demonstrated thick (perifascicular) enhancement on postgadolinium scans. Based on biopsy status we divided the patients into 2 groups: Group A, those in whom biopsy confirmed nLSP; and Group B, those in whom imaging characteristics demonstrated spread despite the lack of a biopsy being performed or negative biopsy results.

For both groups we recorded in detail all available demographic data (age and sex), history (original cancer, initial treatment, initial symptoms, duration, and character and laterality of symptoms), physical examination (pain, weakness, and sensory loss) and electrodiagnostic study findings, details of biopsy, findings on imaging studies including MRI, FDG PET/CT, and ^{11}C -choline PET/CT, evidence of other metastatic disease, further oncological treatment, follow-up status, and appropriate time intervals.

Several cases from the series have been previously described as individual case reports.^{1,9,17,18,27,28,37} The purpose of this article is to review shared anatomical mechanisms and describe common radiological and clinical features.

Results

Group A

History and Evaluation

Ten patients (8 men and 2 women) were included in Group A (prostate cancer $n = 5$, rectal cancer $n = 2$, bladder cancer $n = 2$, cervical cancer $n = 1$). Clinical data for each patient are listed in Table 1. The mean age was 69 years (range 48–85 years). Prior to LSP diagnosis, all patients except 1 underwent surgery, 4 patients received radiotherapy, 3 patients received hormonal therapy with leuprolide, and 2 patients received chemotherapy with other chemotherapeutic agents. Pain was the initial symptom in 7 patients, pain and weakness in 1 patient, and weakness in 1 patient; 1 patient was asymptomatic. In 1 patient the symptoms of LSP preceded the tumor diagnosis by 3 months; in the remaining symptomatic patients the mean time from the original tumor diagnosis to the initial symptom was 60.8 months (range 1 month–18 years). The asymptomatic patient had perineural spread that was discovered incidentally on follow-up imaging studies. On presentation, 9 symptomatic patients had a combination of pain, sensory loss, and weakness predominantly expressed in the L5–S1 dermatomes. Of 9 symptomatic patients, 8 had unilateral symptoms and 1 had bilateral symptoms. Electromyography (EMG) findings were abnormal in all patients available ($n = 8$) and demonstrated LSP in 6 patients and sciatic neuropathy in 2. Six patients had no signs of distant metastatic disease at the time of the LSP diagnosis; 2 patients had metastases in lungs, 1 patient had metastases in the pelvis, and 1 had a solitary metastasis in the liver. All patients underwent biopsy procedures, which confirmed nLSP.

Imaging

Details of the imaging characteristics for all patients ($n = 10$) are listed in Table 2. Occasionally, the nerves demonstrated a nodular appearance suggestive of localized tu-

mor proliferation or perineural spread with “skip lesions.” The sciatic nerve was involved in all 10 cases, and the obturator nerve showed signs of perineural spread in 1 patient. The most frequently affected spinal nerves were L-5 to S-2; 3 patients had intradural extension of the tumor. MRI findings correlated with increased uptake on FDG PET/CT ($n = 4$) and ^{11}C -choline PET/CT ($n = 3$) scans. In 7 patients we found unilaterally thickened perirectal fascia, which was hyperintense on T2-weighted imaging and enhanced after intravenous contrast administration.

Outcome

Seven patients were alive at the time of the last follow-up. In 5 patients with no other metastases, further oncological treatment was initiated. In 3 the radiation therapy was escalated to include the lumbosacral plexus, 1 patient died before further therapy could be started, and in 1 patient information on follow-up therapy was not available. The mean time from the initial symptom to the last follow-up was 51 months (range 1 month–11 years).

Group B

History and Evaluation

Seven patients (6 men and 1 woman) were included in Group B (prostate cancer $n = 4$; rectal cancer $n = 2$, bladder cancer $n = 1$). One patient only had images available; this patient is not included in the clinical data. Clinical data are given in Table 1. The mean age was 64.2 years (range 32–81 years). Prior to LSP diagnosis all patients but 1 underwent surgery, 3 patients underwent radiotherapy, 2 patients received hormonal therapy with leuprolide, and 2 patients underwent chemotherapy with other chemotherapeutic agents. Pain was the initial symptom in 1 patient, pain and sensory loss in 1 patient, pain and weakness in 1 patient, and weakness in 1 patient; 2 patients were asymptomatic. The mean time from the original tumor diagnosis to the initial nerve symptom was 98 months (range 6 months–18 years). On presentation, 2 patients had a combination of pain, sensory loss, and weakness in the L5–S1 distribution, 1 patient had pain and sensory loss in the S-1 distribution, and 1 patient had only pain in the S-1 dermatome. All 4 symptomatic patients had right-sided symptoms; no bilateral disease was observed in Group B. EMG was performed in 2 patients and demonstrated LSP in both patients. One patient had distant metastases together with local spread of rectal cancer to the bladder, and 1 patient with prostate cancer had local spread to the rectum. Two patients underwent biopsy, the findings of which were negative for cancer. One patient deferred the biopsy.

Imaging

Details of the imaging characteristics for all patients ($n = 7$) are listed in Table 2. The most frequently affected spinal nerves were L-5 to S-2; no patient had intradural extension of the tumor. MRI findings correlated with increased uptake on FDG PET/CT ($n = 3$) and ^{11}C -choline PET/CT ($n = 1$) scans. In 1 patient we found a unilaterally thickened perirectal fascia, which was hyperintense on T2-weighted imaging and enhancing after intravenous contrast; in 1 patient this finding was bilateral.

TABLE 1. Overview of clinical data for 17 patients with perineural tumor spread

Case No.	Organ	Age (yrs), Sex	Initial Treatment	Time to Initial Sx From Tumor Dx	Physical Examination					Other			Follow-Up			
					Initial Sx	Laterality	Pain	Weakness	Sensory Loss	EMG	Biopsy Site	Metastases at Time of LSP Dx	Further Treatment	Status	Time From Initial Sx	
Group A																
1	Rectum	48, F	S, ChT	—	None	Rt	No	No	No	NA	S-2 (open)	Lung	RT, ChT	Alive	11 yrs	
2	Rectum	50, M	S	12 mos	Pain	Rt	L-5	Incomplete foot drop	No	NA	Sciatic (open)	Liver	S, RT, ChT	Alive	6 yrs	
3	Prostate	60, M	—	~3 mos*	Pain	Lt	S-1, perianal	Glutei, hamstrings	Saddle anesthesia	LSP (L5–S1)	S-1 (open)	No	RT, HT	Alive	8 yrs	
4	Cervix	61, F	S, RT, ChT	1 mo	Pain	Lt	S-1	Complete sciatic palsy	L5–S1	Sciatic neuropathy distal to biceps femoris branch	Sciatic (open)	No	RT, ChT	Died	11 mos	
5	Prostate	64, M	S, RT, HT	6 yrs	Weakness	Bilat	buttock bilat, rt S-1	Lt sciatic palsy, lt adductors 3/5, rt sciatic 3–4/5, rt adductors 4/5	L-5, S-1 bilat, perianal	Bilat LSP, more left	Sciatic (open)	Pelvis	RT, HT	Alive	2 mos	
6	Prostate	70, M	S, RT, HT	9 yrs	Pain, weakness	Lt	L-5, S-1	Sciatic 4/5	L-5, S-1	LSP (L5–S2)	Sciatic (open)	No	HT	Died	8 yrs, 11 mos	
7	Bladder	71, M	S	7 mos	Pain	Rt	S-1	Hamstrings 3/5, otherwise sciatic 1/5	L-5, S-1	LSP (L5–S2)	L-5 (percutaneous)	No	NA	Alive	4 mos	
8	Prostate	77, M	S, RT, HT	6 yrs	Pain	Rt	S-1	Sciatic 4/5	S-1	LSP (L5–S1)	S-1 (open)	No	HT	Alive	5 yrs, 2 mos	
9	Bladder	83, M	S	3 yrs, 4 mos	Pain	Lt	L-5, S-1	Adductors 3/5, foot dorsiflexion 2/5, plantar flexion 4/5	Distal LLE	LSP (obturator & mild peroneal neuropathy)	Sciatic (open)	Lung	— (died)	Died	1 mo	
10	Prostate	85, M	S	18 yrs	Pain	Rt	L-5, S-1	Sciatic 3-4/5	L-5, S-1	Proximal sciatic neuropathy	Lumbosacral plexus (percutaneous)	No	HT	Alive	1 yr, 10 mos	
Group B																
11	Rectum	32, M	ChT	6 mos	Pain	Rt	S-1	No	No	NA	NA	No	No	Alive	2 yrs, 6 mos	
12	Prostate	66, M	S, RT	9 yrs, 11 mos	No	Rt	No	No	No	NA	NA	Tumor invasion of lateral rectum	HT	Alive	2 mos	
(continued)																

(continued)

TABLE 1. Overview of clinical data for 17 patients with perineural tumor spread (continued)

Case No.	Organ	Age (yrs), Sex	Initial Treatment	Time to Initial Sx From Tumor Dx	Physical Examination					Sensory Loss	EMG	Biopsy Site	Other Metastases at Time of LSP Dx	Further Treatment	Follow-Up	
					Initial Sx	Laterality	Pain	Weakness	Status						Time From Initial Sx	
Group B (continued)																
13	Bladder	66, M	S	—	No	Lt	No	No	No	NA	NA	No	— (died)	Died	0 mos	
14	Rectum	69, F	S, RT, ChT	7 yrs, 10 mos	Weakness	Rt	S-1	Hamstrings 4/5, foot & toe flexion 3–4/5, foot dorsiflexion 3/5, toe extension 2-/5	L5–S1	LSP/proximal sciatic neuropathy	Sciatic (open), negative	3 lung nodules, urinary bladder	ChT	Alive	9 yrs, 5 mos	
15	Prostate	71, M	S, RT, HT	4 yrs, 10 mos	Pain, sensory loss	Rt	S-1	No	S-1	NA	NA	No	No	Died	1 yr, 6 mos	
16	Prostate	81, M	S, HT	18 yrs	Pain, weakness	Rt	L-5	Hamstrings 3/5, foot & toe flexion 1/5, foot dorsiflexion 2/5, toe extension 2/5	L5–S1	Proximal LSP	L-5 DRG, S-1 DRG (open), negative	No	No	Alive	4 yrs	
17	Prostate	NA, M	NA	NA	NA	Lt	NA	NA	NA	NA	NA	NA	NA	NA	NA	

ChT = chemotherapy; Dx = diagnosis; HT = hormonal therapy; LLE = left lower extremity; NA = not available; RT = radiotherapy; S = surgery; Sx = symptom; — = not applicable.

* In Case 3 the lumbosacral plexopathy preceded the primary tumor diagnosis.

Outcome

Four patients were alive at the time of the last follow-up. In 3 patients with no other signs of recurrence or metastatic disease, no further therapy was administered. One of these patients later developed extensive pelvic disease and died a year later. Two patients continued hormonal or chemotherapy, and 1 patient died before further therapy could be started. The mean time from the initial symptom to the last follow-up was 41.8 months (range 2 months–9 years and 5 months).

Discussion

Perineural Spread as a Cause of LSP

Anatomy and Mechanism

In the pelvis, the autonomic visceral innervation is provided by the superior and inferior hypogastric plexuses.^{8,54,62} The superior hypogastric plexus is located below the aortic bifurcation and receives input from sympathetic lumbar splanchnic nerves. Caudally, it is connected to the inferior hypogastric plexus via paired hypogastric nerves.⁵⁴ The inferior hypogastric plexus is a mixed sympathetic and parasympathetic plexus, which is innervated by the parasympathetic pelvic splanchnic nerves derived from the S2–4 spinal nerves and by the sympathetic sacral splanchnic nerves from the sacral sympathetic chain. The inferior hypogastric plexus extends to pelvic organs in the form of the rectal plexus, vesicoureteric plexus, and the uterovaginal plexus in females and prostate plexus in males. The pelvic portion of the ureters receives input from the sympathetic superior hypogastric plexus together with the trigone of the bladder. The ovarian plexus derived from T10–L1 innervates the ovaries and merges caudomedially with the uterovaginal plexus.⁶² The kidneys are supplied by the lateral prolongation of the celiac plexus called the renal plexus, which is derived from the T10–L1 levels. Boundaries between organ plexuses, especially those derived from the inferior hypogastric plexus, are more arbitrary rather than formed by obvious anatomical structures.

As demonstrated in prostate,³⁷ bladder,¹ rectal,¹⁸ and cervical²⁸ cancer, the mechanism of spread is quite unified across different pelvic neoplasms (Fig. 1 and Video 1).

VIDEO 1. Animation of perineural spread. A short video demonstrates spread of prostate cancer (*red*), bladder cancer (*blue*), and rectal cancer (*green*) to the inferior hypogastric plexus and then the “common” pathway of spread (*green*) to the lumbosacral plexus, along the spinal nerves proximally (intradural extension is depicted). Perineural spread can also occur along the sciatic and superior gluteal nerves distally and then along the osseous branches to bony pelvis and along the nerve to the obturator internus to the muscle. Although the spread within and beyond the lumbosacral plexus is demonstrated in sequential steps, in vivo it occurs in all directions simultaneously. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved. Click here to view with Media Player. Click here to view with Quicktime.

The tumor cells infiltrate the inferior hypogastric plexus and spread to the lumbosacral plexus along the splanchnic nerves. From the lumbosacral plexus, cancer can spread distally to branching nerves or proximally to spinal nerves. This applies to the lateral walls and the dome of the bladder as well; tumors invading the bladder trigone spread pre-

TABLE 2. Imaging data for 17 patients with perineural tumor spread

Case No.	Organ	Age (yrs), Sex	Laterality	MRI				FDG PET/CT	Choline PET/CT
		Spinal Nerves		Peripheral Nerves	Intradural Extension	Route of Spread*			
Group A									
1	Rectum	48, F	Rt	L5–S1	Sciatic	No	Yes	NA	NA
2	Rectum	50, M	Rt	S-1	Sciatic	No	No	NA	NA
3	Prostate	60, M	Lt	L5–S3	Intrapelvic sciatic	No	Yes	NA	NA
4	Cervix	61, F	Lt	L5–S3	Sciatic	No	Yes	S-2, sciatic	NA
5	Prostate	64, M	Bilat	S2–3 bilat, L4–S1 rt	Bilat sciatic	Yes	No	Bilat S-1 & sciatic, lt L-5	Bilat S-1 & sciatic, lt L-5
6	Prostate	70, M	Lt	L4–S4	Sciatic	Yes	Yes	NA	NA
7	Bladder	71, M	Rt	L5–S2	Sciatic	No	Yes	NA	NA
8	Prostate	77, M	Rt	S1–3	Intrapelvic sciatic	Yes	No	NA	S-1
9	Bladder	83, M	Lt	L4–S1	Obturator, sciatic	No	Yes	L4–S1	NA
10	Prostate	85, M	Rt	S1–3	Sciatic	No	Yes	Sciatic	Sciatic
Group B									
11	Rectum	32, M	Rt	L5–S1	Sciatic	No	Yes	NA	NA
12	Prostate	66, M	Rt	S2–4	No	No	Yes	NA	Perirectal fascia
13	Bladder	66, M	Lt	L5–S1	Sciatic	No	No	Sciatic, bladder wall, pelvic musculature, hamstrings	NA
14	Rectum	69, F	Rt	L5–S1	Sciatic	No	No	S-1, sciatic	NA
15	Prostate	71, M	Rt	L5–S3	Sciatic	No	No	S2–3, sciatic	Rt sciatic, rt S-2
16	Prostate	81, M	Rt	L4–5	Sciatic	No	No	NA	Negative
17	Prostate	NA, M	Lt	L5–S2	Sciatic	No	No	NA	NA

* Route of spread is represented on MRI studies as thickened perirectal fascia, which is hyperintense on T2-weighted images and enhancing after gadolinium contrast.

dominantly to the lumbar plexus along the lumbar splanchnic nerves and then can again extend beyond the plexus proximally to spinal nerves or even intradurally, or in the opposite direction to the obturator nerve. Theoretically, a similar mechanism could apply to ovarian, testicular, or renal cancer, although that has not been demonstrated yet. In 1 patient (Case 5) the tumor spread from the left spinal nerves to the contralateral spinal nerves, utilizing the dural sac as a bridge.¹⁷

The underlying histological basis for perineural spread is perineural invasion (PNI). PNI is considered a major mode of prostate cancer extension outside the prostate gland⁴⁴ and is present in virtually all prostatectomy specimens with extracapsular spread.⁶⁹ PNI is present in up to 54.8% of surgically treated colorectal cancer cases,⁷⁵ up to 47.7% radical cystectomy specimens for bladder cancer,³⁹ and up to 35.1% cervical cancer cases.²⁰ White et al.⁷⁴ suggested that these numbers might still be underreported unless special stains to highlight nerve tissue are used. The original definition proposed by Batsakis¹³ states that PNI is when the tumor is “in, around and through” the nerve. Liebig et al.⁴¹ proposed that finding tumor cells within any of the 3 layers of the nerve sheath represents PNI. Although the definition of PNI at the tumor site might be a subject for discussion, we consider definition of Liebig et al. sufficient for perineural spread. We advocate that perineural spread has occurred when tumor cells are found within any of the 3 layers of the nerve at a site distant from the

tumor mass and acceptable anatomical explanation supported by indirect evidence (imaging) exists. We further advocate, although arguably, that perineural tumor spread also defines when tumor cells obviously track along the nerves, even without any nerve invasion.

Several theories to explain preferential invasion and growth along nerves have been proposed. The possibility that tumor cells simply follow the path of least resistance is unlikely. Various degrees of intraneural invasion are common, including cases solely confined to the endoneurium;^{28,37} the complex nerve ultrastructure of multiple layers of connective tissue and basal laminae makes intraneural invasion an unlikely path of least resistance.⁴¹ Two other mechanisms are more likely to explain the propensity of some tumors to PNI.

Endoneurium and Perineurium Are Chemically and Biologically Privileged Environments and Provide Sanctuary to Cancer Cells. The inner sanctum of the nerve is protected by the blood-nerve barrier (BNB) similarly as the brain is protected by the blood-brain barrier.⁴⁹ The BNB is composed of several layers of perineurial cells encircling each fascicle and nonleaky capillaries surrounded by specialized pericytes. Perineurial cells are connected with tight junctions, and each cell is enveloped in a basement membrane.⁵¹ The formed perineurial barrier efficiently limits diffusion and cell penetration. Similarly, endoneurial capillaries are lined by nonfenestrated endothelium and are, as well as the pericytes, connected by tight junc-

FIG. 1. Illustration demonstrating the unified mechanism of pelvic cancer spread from the prostate, rectum, bladder, and cervix to the lumbosacral plexus along the pelvic autonomic nerves (the superior and inferior hypogastric plexus) and then beyond the lumbosacral plexus to the bony pelvis and pelvic musculature along the osseous and muscle nerve branches. n. = nerve. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

tions.^{58,61} The formed BNB creates an immunologically^{34,46} and chemically protected environment. Not only this could prevent leukocyte infiltration into the tumor and chemotherapeutic agent delivery, but P-glycoprotein expressed by endothelial cells could be directly responsible for active drug efflux.^{3,56} The resulting “sheltering” is supported by cases of leukemia, which relapsed in peripheral nerves.

Direct Interactions Between Nerves and Cancer Cells Promote Tumor Growth and Survival. Recent research shows that more complex reciprocal signaling between nerves and tumor cells is involved. In prostate cancer, the nerves actively decrease tumor cell apoptosis⁴ and promote proliferation and migration through expressing N-Cam,⁴⁰ bystin,⁵ and Beta-2³² adhesion molecules. The former could be mediated by antiapoptotic caveolin-I produced by the perineurium.⁶ This supports our and others³⁴ observation that the perineurium is the most frequently involved layer (Fig. 2). On the other hand, prostate cancer cells⁷ and rectal cancer cells⁴² promote neurite outgrowth if murine dorsal root ganglion cells are co-cultured with the tumor cells. Most studies are focused on pancreatic¹¹ and prostate cancer, and although we can presume that many cellular mechanisms are shared across various cancers, more research to elucidate PNI and perineural spread in pelvic malignancies is called for.

Clinical Implications

Neoplasms should always be included in the differential diagnosis as a possible cause of progressive LSP, especially in patients with a history of cancer. The primary pelvic malignancy diagnosis was preceded by nerve symptoms in only 1 patient (Case 3). In all other patients the time from the initial tumor diagnosis to LSP varied widely. All patients except for 1 in whom nLSP occurred after 1 year of follow-up after the tumor diagnosis underwent radiation therapy or chemotherapy (hormonal therapy) prior to the development of nLSP. We can presume that these interventions somewhat “salvaged” and delayed cancer progression within the nerves; however, our series is too small to perform any statistical evaluation of effect of different treatments. The risk of misdiagnosis is high, as multiple patients were referred to us as having radiation-induced plexopathy or inflammatory plexopathy. One patient underwent an L3–5 decompressive surgery and fusion at an outside hospital with no relief of symptoms.

In our series and other reported series^{31,67} of nLSP, the most common initial symptom was pain followed by weakness and sensory disturbances. On physical examination, findings from the straight-leg raising test can be positive. More indicative is percussion tenderness along the sciatic nerve if present. Infiltration of the pelvic sym-

FIG. 2. Case 5. Perineural invasion (histopathology). Photomicrograph of a longitudinal section of a sciatic nerve fascicle demonstrating invasion of the endoneurium (arrow) and perineurium (arrowhead) with prostate cancer cells. The specimen was obtained from a fascicular biopsy. H & E, original magnification $\times 100$.

pathetic system can produce “hot and dry foot” syndrome from the lack of perspiration and vasomotor activity.^{21,24} Electrodiagnostic studies can help to localize and objectify the extent of plexus involvement, and myokymic discharges, if present, strongly point toward radiation as the cause of LSP.⁶⁷

Imaging

Imaging is the cornerstone of LSP evaluation. In perineural spread changes are often very subtle with no obvious tumor mass to help differentiation of neoplastic from nonneoplastic origin. Although numerous advanced MR sequences are advocated in the literature, an MRI diagnosis can often be made with standard imaging sequences performed with high resolution. This is best accomplished with 3-T imaging. Unilateral plexus imaging will increase imaging quality; however, we recommend a field of view that includes both plexuses from upper lumbar nerve roots to the sciatic nerve in the thigh. Otherwise, the extent of the disease can be underestimated for future therapy planning. Gradient recalled echo–based sequences (spoiled gradient recalled echo) and T2-based sequences (including fast spin echo) with robust fat suppression have become part of our standardized peripheral nerve imaging protocol in addition to standard T1-weighted sequences. The affected nerves are typically enlarged on T1-weighted sequences, often with irregular and nodular contours (Fig. 3A–C). On T2-weighted images they are hyperintense (Fig. 3D–F), but the T2 signal might extend beyond tumor infiltration due to “downstream” effects. Fat-saturated postgadolinium contrast-enhanced sequences are highly valuable in the evaluation of perineural spread of disease (Fig. 3G–I) and should be performed unless there is a contraindication to gadolinium contrast administration. Affected nerves demonstrate thick, irregular, perifascicular enhancement. In 9 patients we observed an abnormality we consider to represent infiltrated inferior hypogastric plexus, i.e., spread from the organ to the sacral plexus. In 8

patients it was a thickened, hyperintense (on T2-weighted sequences) and heterogeneously enhancing perirectal fascia, unilaterally in 7 patients (Fig. 4A) and bilaterally in 1 patient (Case 12) (Fig. 4B). This simultaneous, “parallel” infiltration of both left and right inferior hypogastric plexuses provides an additional explanation for bilateral nLSP in addition to transdural spread described in Case 5 (Fig. 4C).¹⁷ In 1 patient we found a linear abnormality running more cranially toward the lumbar plexus. Consistent with the known innervation of the bladder, this patient presented with obturator nerve symptoms.¹

Interpretation of the MRI after pelvic radiation may be challenging. In radiation-induced LSP the nerves might be enlarged but typically less than that seen in perineural tumor spread, hyperintense on T2-weighted images, and enhancing after gadolinium administration. The enhancement in radiation fibrosis is classically linear and homogeneous as opposed to the nodular and infiltrative appearance typical of PNI. The changes correspond to the radiation port. The nerves can be surrounded by fibrotic tissue producing fine, diffuse reticular enhancement, again confined to the irradiated area.

Positron emission tomography can be a very useful imaging method and support neoplastic nature if positive. No definite standard uptake value has been established in peripheral nerve evaluation; we use surrounding muscles as a reference. Our experience shows that in prostate cancer patients, studies using FDG provide superior sensitivity to ¹¹C-choline scans (Fig. 5). This could be explained by the BNB, which limits choline diffusion²² into the nerves or nonselective uptake of FDG by nonneoplastic (e.g., inflammatory cells). Bartels et al.¹² reported a case very similar to ours with very avid uptake of FDG in the lumbosacral plexus, but which was concluded as inflammatory due to low positivity on the Choline PET/CT scan. We wonder if this case could in fact be neoplastic in nature.

Diagnosis and Outcome

The ultimate confirmation of tumor invasion is provided by biopsy, which we recommend to perform in all patients in whom a positive result might alter subsequent therapy. Whether to use an open or percutaneous approach is not clear. Open biopsy can help to select pathologically appearing tissue and increase yield, but it will increase risk.¹⁴ Open biopsy also provides a larger sample and allows for more detailed evaluation of the degree of intraneural invasion. Important in biopsy site selection is high-quality imaging and accurate interpretation. Importantly, it should be kept in mind that a negative biopsy result does not exclude cancer, as demonstrated in Cases 14 and 16. Negative biopsy results can be explained by the relative occult nature of the neoplastic infiltration at operation, skip lesions, by biopsying the wrong portion of the nerve, or by associated pathology as acknowledged in *Limitations*. In 2 patients with negative biopsy results, inflammation with increase in endoneurial (Case 14) or surrounding (Case 16) collagen was present, but these changes were very nonspecific and did not allow us to conclude an alternate diagnosis. Percutaneous biopsy can on occasion be done of a “mass-like” expansion of nerve (Case 7).

Once the diagnosis of nLSP is established, the treat-

FIG. 3. MRI appearance of perineural tumor spread along the lumbosacral plexus. Axial T1-weighted images demonstrate enlarged sciatic (arrowhead in A), obturator (arrowhead in B), and L-5 and S-1 spinal nerves (arrowheads, C). Axial T2-weighted fat-suppressed images at the same levels show enlarged, hyperintense, and heterogeneous nerves (sciatic, obturator, spinal nerves, arrowheads in D, E, and F, respectively). Axial spoiled gradient echo recalled images after intravenous gadolinium contrast visualize the same nerves at the same levels demonstrating avid, heterogeneous and preferential perifascicular enhancement (sciatic, obturator, and spinal nerves, arrowheads in G, H, and I, respectively).

ment currently does not change based on the underlying mechanism. Although visceral nerves could be sacrificed to some extent without a major impact on quality of life, the same cannot be said about major components of the LSP. In the biopsy-proven group (Group A), the diagnosis of nLSP led to therapy modification in 8 patients. In Group B, no significant modification of therapy was made, but one patient who elected not to undergo biopsy later developed posterior pelvic wall recurrence and hydronephrosis and died a year later (Case 15). The role of the BNB in chemotherapy is yet to be established.

A review of the literature to explain reported prostate, rectal, bladder, and cervical cancers causing nLSP have been previously published.^{1,9,17,18,27,37} We wonder if our theory could explain nerve symptoms in other types of cancer that were not previously discussed. Uchida et al.⁶⁸ reported on a patient of uterine carcinoma who presented 4 years later with metastases to S-1 and S-2 spinal nerves and nerve roots. Cho et al.¹⁹ described a patient with a history of locally invasive squamous cell carcinoma of the anus. Ten months after diagnosis and resection, the patient pre-

sented with weaker quadriceps femoris muscle, diminished patellar and Achilles tendon reflexes, and intradural cauda equina metastasis. Johnson and Pomeroy³³ reported 2 cases of Ewing's sarcoma that recurred at the margin of the radiation field "with tumor extending along the nerve roots of the lumbosacral plexus." Wald and Roland⁷¹ published a similar case of Ewing's sarcoma metastasis to a single nerve root, probably sensory, as stimulation did not produce any muscle contraction. Although kidneys are not exactly pelvic organs, several authors published cases suggestive of the same mechanism. Kubota et al.³⁶ reported a case of renal cell carcinoma that metastasized to a single nerve root at the L-3 level; we wonder if this and several other cases of "metastatic" renal cell carcinoma to cauda equina^{2,25,43,52,65} could be explained by perineural spread.

Perineural Spread Beyond the Lumbosacral Plexus

Once tumor is within the lumbosacral plexus, it can continue to spread in the distal as well as proximal di-

FIG. 4. Axial gadolinium-enhanced SPGR image of the pelvis, showing the unilaterally enlarged and enhancing perirectal fascia, presumably representing perineural spread of cervical cancer from the uterus to the lumbosacral plexus along pelvic autonomic nerves (*dashed arrow in A*). Similar mechanism of spread can occur bilaterally (*dashed arrows in B*) and provide a theoretical explanation for bilateral symptoms in nLSP as demonstrated in an axial gadolinium-enhanced SPGR image of a patient with prostate cancer (*B*, the *white dot* represents the prostate gland). A coronal T2-weighted fat saturated image demonstrates another mechanism of bilateral neoplastic plexopathy caused by perineural spread: a transdural spread of tumor between the opposing spinal nerves (*dashed arrow in C*).

rection. Perineural spread along the muscle and osseous nerve branches has been proposed as an alternate explanation for muscle¹⁵ and bone¹⁶ metastases. This mechanism could explain cases of prostate cancer with nerve symptoms and regional bone metastases,^{26,50,70} or bladder with muscle metastases.⁴⁷ Although muscle is by nature very resistant to metastasis,⁶⁰ in these patients the resistance may decrease as the muscle becomes denervated.⁷³ Cancer cells can spread proximally onto the dural sac¹⁷ or even intradurally, which was observed in 3 patients in our series. Prostate-specific antigen levels in the CSF have been proposed to confirm and monitor CNS involvement in prostate cancer.^{48,59} We measured the prostate-specific antigen in CSF in Case 5, which was nearly 10 times higher than in serum.¹⁷ We theorize that cancer cells can subsequently seed within CSF, providing an alternate explanation for CNS metastases. Lefresne et al.³⁸ reported a case of dura-based metastases at the T-4 and L4–5 levels with foraminal extension. Although the L4–5 metastasis was discovered later, we wonder if this case could be explained by perineural spread and subsequent intradural seeding, only with the L4–5 tumor lesion being somewhat salvaged and delayed by previous radiotherapy.

Perineural Spread to Other Organs

Warren et al.⁷² reported a case of prostate cancer with

tumor masses lateral to the rectum with PNI and invasion of muscularis propria with PNI and even with tumor in anal submucosa, where PNI was “striking and fairly constant.” Although the patient had locally advanced disease, it is clear that invasion of the rectum occurred preferentially along the nerves. We can report a similar observation in Case 12, although the diagnosis was only based on imaging (Fig. 6). If PNI is the main form of extraprostatic tumor extension, we wonder how many cases of bladder metastases of prostate cancer used nerves as a preferential mean of invasion,⁵⁷ or how many cases of 1) cervical cancer metastases to the rectum or bladder,¹⁰ 2) bladder cancer to the prostate,^{23,43} or 3) rectal cancer to the prostate or bladder⁵³ occurred along the nerves.

Perineural Spread as an Initial Step in Systemic Disease

Kayahara et al.³⁵ demonstrated perineural extension of pancreatic cancer to a lymph node, which could explain why lymph node metastases of pancreatic cancer correlate with PNI rather than with lymphatic vessel invasion.⁶⁶ Similar observations have been reported for prostate,⁶⁴ rectal,^{29,55} and bladder³⁹ cancer. We wonder if perineural extension could be an initial step to lymphogenous and potentially hematogenous spread thus leading to systemically disseminated disease.

Limitations

Although the perineural spread theory is the proposed anatomical explanation for cases in our series and selected cases in the literature, we acknowledge that other possible explanations exist. Cancer can spread hematogenously to very unusual locations including peripheral nerves. Our explanation applies to selected cases in which we find the imaging evidence very compelling. Although the endoneurium and perineurium lack lymphatic channels,⁴¹ we cannot exclude the possibility that the lymphatic system “approximated” cancer to the lumbosacral plexus. Another limitation is that 7 cases did not have histological confirmation, in which LSP might have been caused by unrelated pathology despite cancer history. We understand that final confirmation of our theory would be provided only by histopathological examination of the entire pathway from the organ to the plexus and beyond. Also, since we do not have the original radiation maps and we do not know what exact area was irradiated, we cannot comment on the efficacy of radiation therapy or propose any modifications in the initial oncological treatment.

Conclusions

We provide a unifying theory to explain LSP in selected cases of various pelvic neoplasms (prostate, bladder, cervical, and rectal cancer). Tumor cells can use splanchnic nerves as conduits and spread from the end organ to the lumbosacral plexus. From there, the cancer cells can continue proximally to the spinal nerves, intradurally, and to the contralateral plexus. Theoretically once they reach intradural space, they can seed and cause CNS metastases. Distally, the tumor spreads to the branching nerves as the sciatic or obturator nerves and along muscle and osseous branches to innervated muscles and bones. Clinically

FIG. 5. FDG versus Choline PET/CT in perineural spread of prostate cancer. Based on our experience, in prostate cancer imaging FDG provides superior sensitivity to ^{11}C -choline as demonstrated by axial composite FDG PET/CT (**A and C**) and Choline PET/CT (**B and D**) images. The FDG PET/CT showed higher standard uptake values in the affected sciatic nerve (dashed circle in **A**) and in the intradural tumor extension (arrowhead in **C**) than comparable scans utilizing choline (dashed circle in **B**; arrowhead in **D**).

these patients present with pain followed by weakness and numbness, and although the clinical pattern is consistent with previously reported series of nLSP, in our series without significant tumor bulk the disease progressed sig-

nificantly more slowly. Radiological studies show a subtle, reproducible pattern. We demonstrated that our proposed mechanism is applicable to other pelvic neoplasms (anal cancer, Ewing sarcoma) for which perineural spread has not been previously described.

FIG. 6. Perineural spread of prostate cancer to the rectum. An axial gadolinium-enhanced LAVA-flex image demonstrates pararectal "metastases" of prostate cancer with invasion of rectal wall (arrowheads in **A**). An axial composite Choline PET/CT image shows increased uptake in the corresponding areas (arrowheads in **B**).

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Spinner. Study supervision: all authors.

Supplemental Information

Videos

Video 1, Media Player. http://mfile.akamai.com/21490/wmv/digitalwbc.download.akamai.com/21492/wm.digitalsource-national/focus15-209_video_1.asx.

Video 1, Quicktime. http://mfile.akamai.com/21488/mov/digitalwbc.download.akamai.com/21492/qt.digitalsource-global/focus15-209_video_1.mov.

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