

A Literature Review of Dorsal Root Entry Zone Complex (DREZC) Lesions: Integration of Translational Data for an Evolution to More Accurate Nomenclature

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Abstract: The purpose of this translational review was to provide evidence to support the natural evolution of the nomenclature of neuromodulatory and neuroablative radiofrequency lesions for pain management from lesions of individualized components of the linear dorsal afferent pathway to “Dorsal Root Entry Zone Complex (DREZC) lesions.” Literature review was performed to collate anatomic and procedural data and correlate these data to clinical outcomes. There is ample evidence that the individual components of the DREZC (the dorsal rami and its branches, the dorsal root ganglia, the dorsal rootlets, and the dorsal root entry zone) vary dramatically between vertebral levels and individual patients. Procedurally, fluoroscopy, the most commonly utilized technology is a 2-dimensional x-ray-based technology without the ability to accurately locate any one component of the DREZC dorsal afferent pathway, which results in clinical inaccuracies when naming each lesion. Despite the inherent anatomic variability and these procedural limitations, the expected poor clinical outcomes that might follow such nomenclature inaccuracies have not been shown to be prominent, likely because these are all lesions of the same anatomically linear sensory pathway, the DREZC, whereby a lesion in any one part of the pathway would be expected to interrupt sensory transmission of pain to all subsequent more proximal segments. Given that the common clinically available tools (fluoroscopy) are inaccurate to localize each component of the DREZC, it would be inappropriate to continue to erroneously refer to these lesions as lesions of individual components, when the more accurate “DREZC lesions” designation can be utilized. Hence, to avoid inaccuracies in nomenclature and until more accurate imaging technology is commonly utilized, the evidence herein supports the proposed change to this more sensitive and inclusive nomenclature, “DREZC lesions.”

Keywords: pulsed radiofrequency treatment, DREZ, radiofrequency ablation, chronic pain, ganglia, spinal

Introduction

The objective of this manuscript is to provide evidence for a proposed transition in nomenclature for a milieu of similar pain management procedures to the more accurate and encompassing name, Dorsal Root Entry Zone Complex (DREZC) lesions. Chronic pain is more prevalent in the USA than cancer, cardiac disease, and diabetes combined, affecting over 100 million Americans with a financial burden ranging from \$560 to \$635 billion in 2010 US dollars,¹ and pain management procedures play a major role in the care of these patients. Anatomically, pain transmission is perceived through the

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dorsal afferent pathways, which begin with extraspinal peripheral nerve branches like the medial, intermediate, or lateral branches, which connect to the spinal nerves (SN), and propagate painful signals through the dorsal roots (DR) along the dorsal afferent pathway. The DR then propagate that afferent signal to the dorsal root ganglia (DRG) and, subsequently, to the dorsal rootlets (DRL) and, then, to the dorsal root entry zone (DREZ), herein collectively termed the Dorsal Root Entry Zone Complex (DREZC) (Figure 1).²⁻⁷

Neuroablative and/or neuromodulatory radiofrequency lesions have been utilized to lesion each of the DREZC components, from the distal branches to the DREZ itself.⁸⁻¹¹ The

DREZC is a linear conducting system, in which any anatomic or functional lesion in any one component will interrupt the transmission of pain to all subsequent more proximal segments.¹¹⁻¹⁸ Thus, we propose a transition of nomenclature to refer to these lesions collectively as, DREZC lesions.

Unfortunately, the nomenclature has been traditionally diverse, identifying lesions of each component of the DREZC as separate procedures, rather than lesions of the same linear DREZC afferent pathway. This is fraught with several fallacies as outlined below. Thus, the objective of this narrative review is to integrate translational data (anatomic and clinical) to support the natural evolution of the

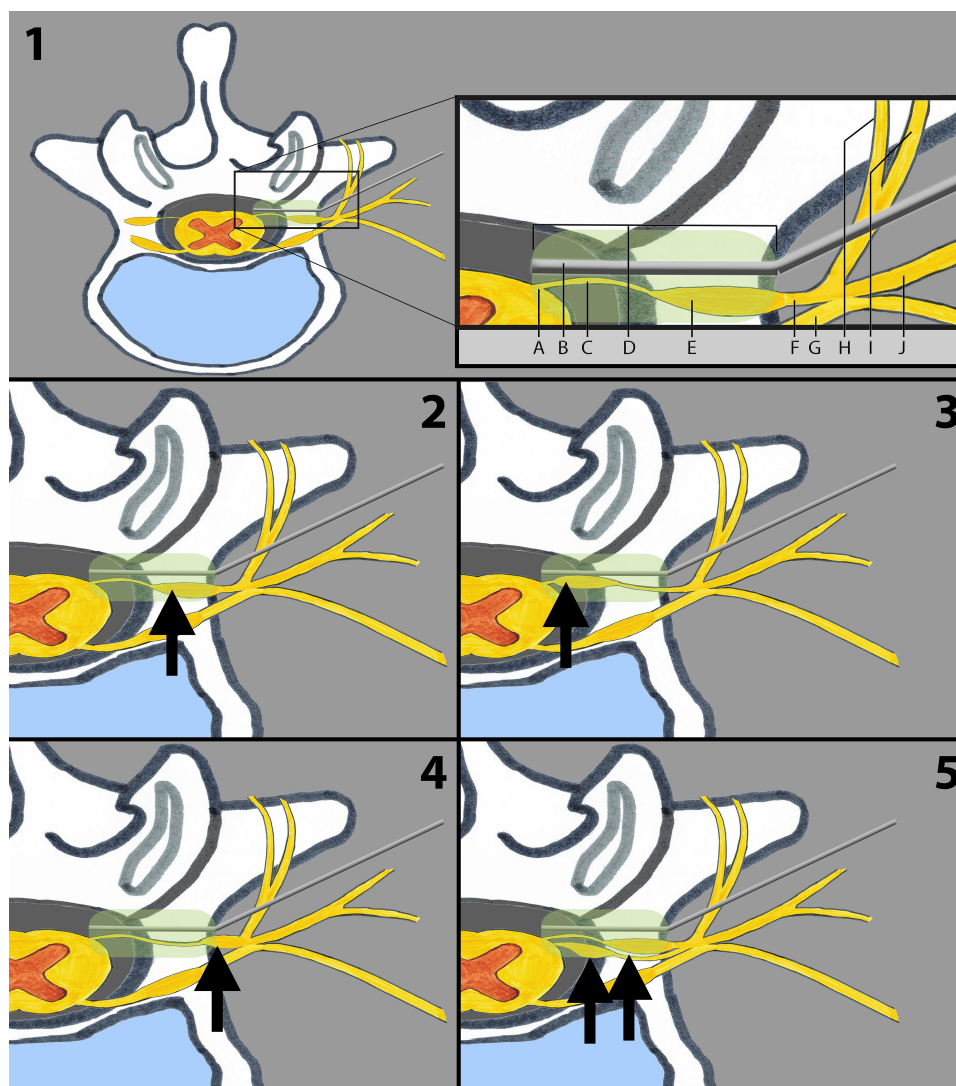


Figure 1 Schematic of variability of dorsal root entry zone complex (DREZC) anatomy in correlation to typical radiofrequency cannula anatomic position. 1. Lumbar vertebra with spinal cord and sensory afferent pathway segments with magnified and labeled view box to the right side. The dorsal root entry zone complex (DREZC) is composed of components labelled A, C, E, and F. A. Dorsal Root Entry Zone (DREZ). B. Radiofrequency (RF) cannula in typical position, adjacent to the DREZC. C. Dorsal Rootlets (DRL). Herein artistically depicted as one line, but DRL can vary in number to as many as 15 DRL per DREZC. D. The anatomic distribution of the energy wave emitted by the RF cannula. E. Dorsal Root Ganglion (DRG). F. Dorsal root (DR). G. Ventral root. H. Medial branch. I. Intermediate branch. J. Lateral branch. 2-5 show variability in anatomic position and number of DRG relative to the vertebra and RF cannula. Arrow depicts DRG. 2. Intraforaminal DRG anatomy. 3. Intraspinal DRG anatomy. 4. Extraforaminal DRG anatomy. 5. DRG Biganglionic anatomy.

nomenclature from lesions of individualized components of the DREZC to, henceforth, refer to these neuroablative and/or neuromodulatory radiofrequency lesions of the DREZC as, “DREZC lesions.”

Methods

Search Strategy

A literature search with PUBMED was carried out with publication date range from inception to March 1, 2020, with the following search terms: “DREZ” (317 reports); (“Ganglia, Spinal”[Mesh]) AND “Spinal Canal”[Mesh] (22 reports); “dorsal root foraminal anatomy” (146 reports); “dorsal root ganglion foraminal anatomy” (31 reports); “pulsed radiofrequency dorsal root” (142 reports); and “radiofrequency dorsal root ganglion,” (187 reports). In addition, bibliographies of retrieved literature were cross-referenced to identify reports omitted from search terms mentioned above. This was not a systematic review, nor was it intended as such. Rather, the purpose of the search was to combine the anatomic data (linear dorsal sensory pathway, of which a lesion at any point would result in a disruption of sensory transmission through the same linear pathway) with clinical data to support or refute the physiologic hypothesis that a lesion of any part of a linear sensory pathway would result in disruption of painful neural sensory transmission.

Inclusion Criteria

Only English language publications were considered. Those describing anatomic findings relating to components of the DREZC (Figure 1) were considered. Reports related to procedural outcomes relating to lesions of the dorsal afferent pathway were also included. Using the PICOS method, clinical data were considered if they described a population of patient for any pain indication; underwent RF lesioning of any component of the DREZC, regardless of whether or not a comparative treatment was described; and inclusive of all clinical patient outcomes described, both positive and negative. Study type was not limited by study design, although only human data were included.

Exclusion Criteria

Non-English language publications and animal data were excluded.

Data Collection

Once duplicate publications were deleted, reports were screened for eligibility. Those with data applicable to the

objective described above were utilized. Data that met inclusion and exclusion criteria and were relevant to the Outcomes Measured described below were extracted from these documents by all three authors and collated. Discrepancies in data extracted were resolved through discussion between the authors.

Outcomes Measured

Anatomic variability data were identified and documented for each segment of the DREZC (Figure 1), including data regarding size, shape, number, and location of each DRG, DR, and VR. Clinical outcomes for neuroablative and/or neuromodulatory procedures involving the DREZC components (Figure 1), both positive and negative, were included when the data were available, with rate of successful analgesia considered as the primary outcome for clinical data, irrespective of how analgesia was measured. Data presenting scales for pain and functional change were considered, but no attempt was made to tabulate or compare scale-based data to the binary data of “success” or “failure” to achieve analgesia post-procedure. No quantifiable analyses were performed or intended.

Results

A total of 858 studies were found using the search strategy, including reports identified through bibliographic review. Seventy-two were retained for inclusion herein. Publications spanned 1980 to 2019.

Procedural and Anatomic Data

First, there is significant variability in the anatomy of individual components of the DREZC, not just from individual person to person, but at each spinal level within the same person. The number of DR and DRGs per spinal level have been found to vary from 1 to 3 ipsilateral DRGs per spinal level (Tables 1 and 2).^{19–21} The DRG size has been found to vary between spinal levels as well.^{22–24} Similarly, the locations of DRGs in relation to their respective foraminae –

Table 1 Analysis of Dorsal and Ventral Root Anatomy at the Intervertebral Foramina (L4 and L5): Singular or Bifurcating¹⁹

Number of Roots/Ganglia	n (%) (of 88 Samples)
1 DRG	69/88 (78.4)
2 DRGs	19/88 (21.6)
1 DR	69/88 (78.4)
2 DRs	19/88 (21.6)
1 VR	3/88 (3.4)
2 VRs	85/88 (96.6)

Abbreviations: DRG, dorsal root ganglia; DR, dorsal root; VR, ventral root.

Table 2 Percentage of Singular DRG, Biganglia and Triganglia Seen at Lumbar Dorsal Root^{19,20}

Dorsal Root	Singular DRG	Biganglia	Triganglia
L1	95.2%	4.8%	0.0%
L2	72.6%	26.1%	1.3%
L3	55.2%	43.9%	0.9%
L4	41.3%	58.0%	0.8%
L5	71.5%	27%	1.5%

intraspinal, foraminal, or extraforaminal – were also found to vary significantly at each spinal segment (Figures 2 and 3).^{19–21,23,25–31} This variable location within the DREZC results in a relative change in the adjacent DR and DRL segments (Figure 1). Furthermore, the number of DRLs was found to range from 2 to 15, depending on spinal level,^{2,5,21,24,32–35} and the location and size of the DREZ itself, compared to midline and the posterolateral sulcus, was also found to be variable.^{2,5,24,32,34}

Secondly, and perhaps most importantly, the intra-procedural imaging technology typically utilized to target individual components of the DREZC during radiofrequency procedures is fluoroscopy. Fluoroscopy is limited in its capacity to identify individual components of the DREZC (Figure 4).^{8,12,36} Fluoroscopy utilizes tubular x-ray technology, a 2-dimensional modality that cannot directly visualize nervous tissue at any component of the DREZC, but does allow for visualization of bony architecture, which allows the physician to approximate the position of the radiofrequency cannula tip to the target lesion.⁸ This approximation does not guarantee accurate

placement of the cannula tip adjacent to any one component of the DREZC.

Clinical Correlation

Hence, when this anatomic diversity is taken into account in the context of the limited capacity of the most commonly utilized intra-procedural imaging technology (fluoroscopy) to identify individual segments of the DREZC, the logical presumption might be that radiofrequency lesions of the DREZC may be fraught with high failure rates, and that the more invasive classic surgical DREZ lesion may provide better outcomes. Conversely, however, outcomes for both non-surgical ablative³⁷ and non-surgical neuromodulatory⁹ radiofrequency lesions are generally favorable (Figure 5), while the more invasive surgical approach was fraught with complications (Table 3) and a comparable degree of analgesia (Figure 6). Moreover, an analysis of cannula tip placement in relation to the pedicle and foramen showed that neuromodulatory pulsed radiofrequency outcomes were similarly successful in treating lumbar radicular pain irrespective of cannula position (intraspinal, deep to the pedicle, versus extraforaminal, outside of pedicle), even though this modality (x-rays) cannot accurately localize the cannula tip to any one targeted component of the DREZC.³⁸

The more invasive classic surgical DREZotomy procedure utilizes microsurgical dissection to visualize the target lesions, then utilizes similar radiofrequency ablative cannulas to induce finite lesions through a 1–2mm active tip.^{15,17,39,40} Despite the careful planning and surgical

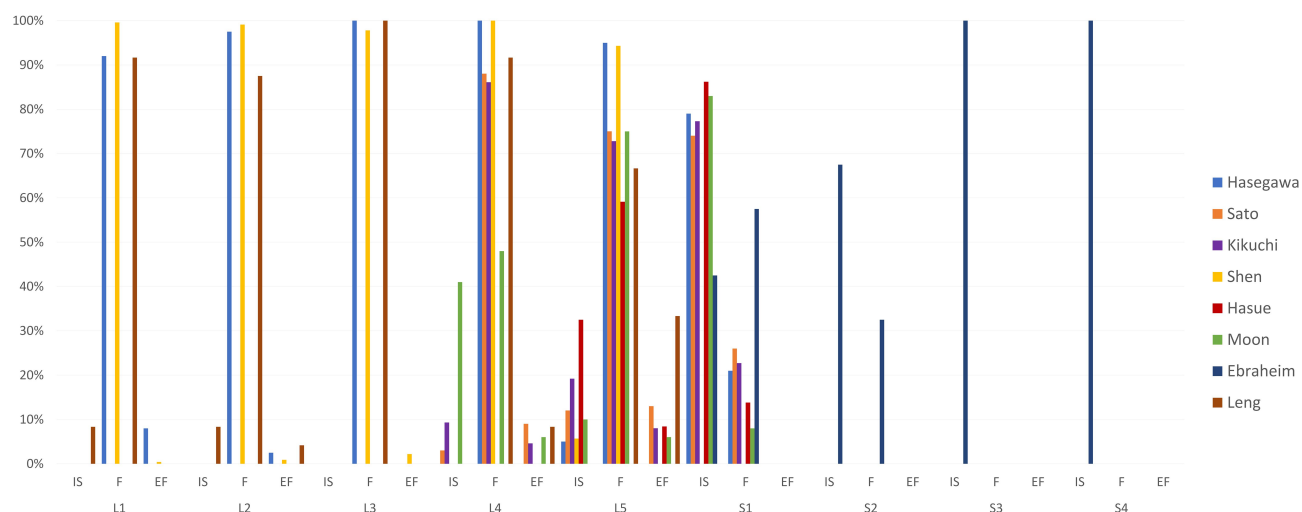


Figure 2 DRG-foraminal anatomy from L1 through S4 spinal levels.
Abbreviations: IS, intraspinal; F, foraminal; EF, extraforaminal.

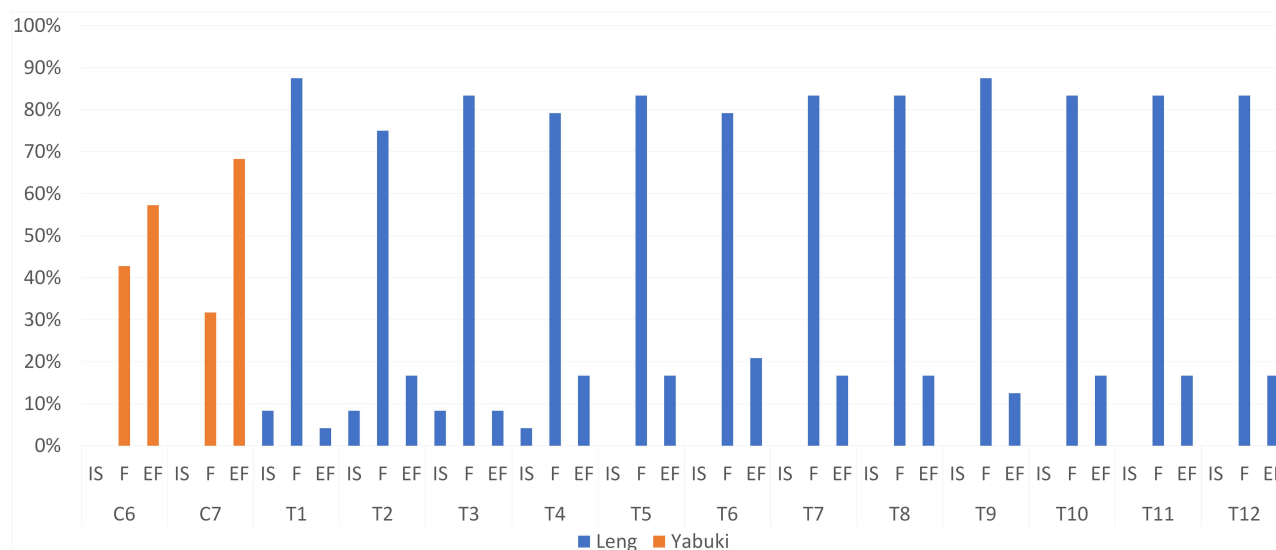


Figure 3 DRG-foraminal anatomy from C6 through T12 spinal levels.

Note: C8 DRG anatomy not described in source data.

Abbreviations: IS, intraspinal; F, foraminal; EF, extraforaminal.

dissection for direct visualization and localization, most studies report significant failure rate to achieve adequate analgesia (Figure 6), with numerous complications (Table 3). One explanation for these surgical failure rates may be due to the lack of intra-operative nerve stimulation for

localization in all cases. Intra-operative nerve stimulation has shown that stimulation of the DREZ fails to evoke a response in some patients, emphasizing that dorsolateral stimulation resulted in larger amplitude spinal cord evoked potentials than did dorsal stimulation.^{41,42} Tomas et al showed that intraoperative stimulation resulted in significantly better pain relief than when no nerve stimulation was used (odds ratio = 10).⁴³ Others have also showed improved outcomes when neurostimulation is utilized intraoperatively.⁴⁴

Similar neurosensory stimulation is used intra-procedurally for fluoroscopically guided radiofrequency lesions of the DREZC (Figure 4), to localize the dorsal sensory pathways, prior to treatment with application of either pulsed or continuous radiofrequency energy to the DREZC.^{9,14,45–52} A similar process is utilized during surgical implantation of DRG stimulators.⁵³ Irrespective of the procedure being performed, this neurosensory stimulation is a process non-specific to any one component of the DREZC, as any component within this linear sensory pathway will transmit a similar positive sensory response as any adjacent segment of the DREZC.¹¹ This positive correlation between sensory capture and positive clinical outcomes is a direct reflection of sensory capture of the DREZC, rather than capture of any one component alone.

It is also important to note that there are differences in safety favoring the fluoroscopically guided minimally invasive DREZC lesion approach. Compared to the

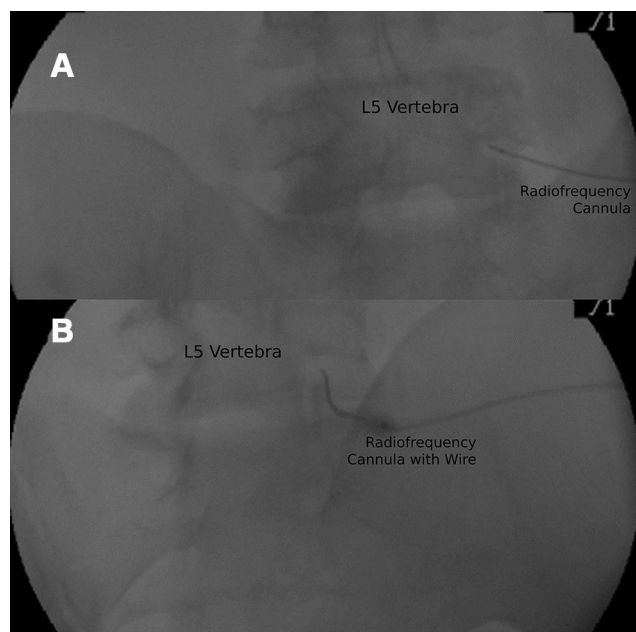


Figure 4 Fluoroscopic image of a radiofrequency needle placement and wire insertion for neurosensory stimulation prior to neuromodulatory pulsed radiofrequency right L5 DREZC lesion. (A) Posteroanterior fluoroscopic view. (B) Right oblique fluoroscopic view – 25°. Deidentified image obtained from Dr. Visnjevac with documented patient consent.

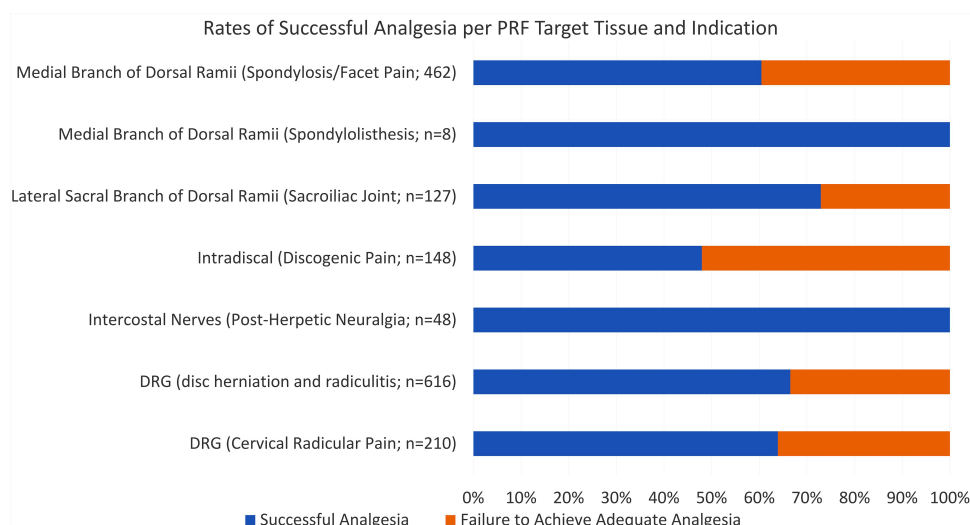


Figure 5 Pulsed radiofrequency DREZC lesion success and failure rates to achieve adequate analgesia per indication. Extrapolated from, Facchini G, Spinnato P, Guglielmi G, Albinini U, Bazzocchi A. A comprehensive review of pulsed radiofrequency in the treatment of pain associated with different spinal conditions. *Br J Radiol* 2017; 90: 20,150,406.⁹

surgically induced structural lesions using higher temperature continuous radiofrequency thermocoagulation of the DREZ, itself, pulsed radiofrequency of the DREZC has been utilized as a non-ablative, neuromodulatory method, of treating neuropathic pain^{9,54–57} with comparable success rates (Figure 5)^{9,38,58} to surgical DREZ lesions (Figure 6).

Discussion

The purpose of this translational review was to provide evidence in the support of the natural evolution of the nomenclature of radiofrequency lesions from lesions of individualized components of the dorsal afferent pathway to, henceforth, refer to these neuroablative and/or neuromodulatory radiofrequency lesions of this linear pathway as, “Dorsal Root Entry Zone Complex (DREZC) lesions.” Although current nomenclature is presumptively precise to each individual lesion, the clinical imaging tools commonly utilized in clinical practice do not allow for it to be as accurate as the new “DREZC lesions” nomenclature. This nomenclature transition is supported by the following evidence as outlined herein:

(a) There is a high degree of anatomic variability of the dorsal root ganglia, varying in number from 1 to 3 per spinal level (Tables 1 and 2), and in their locations relative to their respective foramina (Figures 2 and 3).

(b) The number of DRLs was found to range from 2 to 15, depending on spinal level,^{2,5,21,24,32–35} and the location and size of the DREZ itself, compared to midline and the

posterolateral sulcus, was also found to be variable.^{2,5,24,32,34}

(c) The use of fluoroscopy does not and cannot identify individual components of the DREZC (Figures 1 and 4).^{8,11}

(d) The radiofrequency cannula tip position compared to the DRG did not impact the efficacy of pulsed radiofrequency lesions of the DREZC.³⁸

(e) There is evidence that the more procedurally accessible dorsolateral, rather than dorsal columns, intraoperative nerve stimulation yield better outcomes^{2,41–43} (note: the dorsolateral cord communicates with the DRLs and the more distal portions of the DREZC⁵).

Intraoperatively, both surgical exposure with direct visualization and the use of fluoroscopy have their limitations with resultant failure rates (Figures 5 and 6, Table 3). When neurosensory mapping is used to supplement surgical exposure of fluoroscopic imaging to identify the dorsal segments correlating with the patient’s pain, the technology utilized for neurosensory mapping does not itself differentiate between the individual DREZC components, and yet efficacy is not compromised,^{38,43,44,53} further supporting the assertion for the nomenclature to rightfully evolve to the more sensitive and inclusive terminology, “DREZC lesions.”

This improved accuracy in nomenclature will, inherently, be limited by a loss of precision as each component of the DREZC would no longer be presumptively labelled. Such a nomenclature change does not, however, prevent more specific anatomic or clinical

Table 3 Transient and Serious or Long-Term Complications Following DREZ Surgical Lesions

Post-Operative Complications Following Surgical DREZ Lesioning		
Author (Date)	Transient Complications	Severe or Lasting Complications
Bing (2019) ⁶⁰	10 of 42: diffuse pruritis (average 3 days), symptoms alleviated through low-dose intramuscular injection	3 of 42: permanent tingling pain affecting daily life, 2 of which had resolution with adjacent level DREZ lesions; 1 remanded to oral analgesics
	2 of 42: wound dehiscence	1 of 42: recurrence of pain in the original pain area that increasingly worsened
	1 of 42: urinary tract infection	
Takai (2017) ⁶¹	1 of 10: sensory deficit, resolved within 1 month	1 of 10: a new persistent pain requiring oral analgesics
	2 of 10: new adjacent level pain for <1 month	
Chivukula (2015) ¹⁰	1 of 83: atelectasis	3 of 83: paresis
	2 of 83: post-op colitis	3 of 83: neuropathy/radiculopathy
		2 of 83: persistent incisional site pain
Ko (2016) ⁶²	None reported	None reported
Awad (2013) ⁶³	None reported	2 of 19: motor weakness
Ruiz-Juretschke (2011) ¹⁶	3 of 18: transient proprioceptive sensory disturbance	1 of 18: death 9 days post-operatively following nosocomial pneumonia
	2 of 18: CSF leak	1 of 18: dorsal post-surgical myelopathy treated with bilateral low dorsal DREZ surgical lesions
Zhang (2008) ⁶⁴	13 of 23: transient hyperalgesia in the upper chest, secondary to prolonged operative positioning	8 of 23: transient slight hemiplegia
		15 of 23: hypesthesia and paresthesia
		6 of 23: a bearing down feeling of affected extremity
		4 of 23: deep sensory disability in the lower limbs
Tomas (2005) ⁴³	None reported	2 of 21: sustained motor deficits
		1 of 21: sustained sensory deficits
Sindou (2001) ⁶⁵	3 of 44: CSF leak	1 of 44: bacteremia
	2 of 44: wound infection	
	1 of 44: subcutaneous hematoma	
Samii (2001) ⁶⁶	None reported	2 of 47: subdural hematoma
		7 of 47: motor weakness
Edgar (1993) ⁴⁰	3 of 112: CSF leak	2 of 112: sensory deficits
	5 of 112: myelopathic myoclonus	3 of 112: motor deficits
		1 of 112: spine instability
		2 of 112: pulmonary embolus
		8 of 112: treatment failure (no analgesia)
		2 of 112: suicide 1–2 years post operatively

(Continued)

Table 3 (Continued).

Post-Operative Complications Following Surgical DREZ Lesioning		
Author (Date)	Transient Complications	Severe or Lasting Complications
Kumagai (1992) ⁶⁷	None reported	12 of 15: Sensory loss
		7 of 15: motor weakness
		4 of 15: paraesthesia
		6 of 15: a new pain
Young (1990) ⁶⁸	None reported	1 of 78 patients: reduced sensation, paraparesis, and altered sphincter function.
		1 of 78 patients: bowel and bladder incontinence
		1 of 78 patients: near complete paraplegia
		7 of 78 ipsilateral leg weakness
		7 of 78: loss of proprioception
Campbell (1988) ⁶⁹	2 of 10 patients: hyperreflexia	None reported
Garcia-March (1987) ⁷⁰	1 of 11 patients: transient weakness	None reported
Thomas (1984) ⁷¹	7 of 19: motor weakness	1 of 19: severe motor weakness
	5 of 19: sensory deficits (mostly proprioception)	Some patients had persistent sensory deficits (details unclear)
Samii (1984) ⁶⁶	9 of 35: sensory deficits	None
	1 of 35: motor deficits	
	8 of 35: motor and sensory deficits	
Richter (1984) ⁷²	1 of 10: transient weakness	2 of 10: died post-operatively
		1 of 10: Brown-Sequard type hypoesthesia
		2 of 10: Unilateral hypoesthesia
		1 of 10: motor and sensory deficits

investigation, if future imaging advancements provide for more accurate localization of individual DREZC components, or if new lesioning techniques are developed.

Furthermore, the classic segmental nomenclature, in its current form, does not allow for effective research and comparison of the milieu of procedures noted above, all of which refer to RF lesions of the same linear sensory pathway. Irrespective of advances in the accuracy of imaging technologies, which may be able to identify individual component of the DREZC, this proposed nomenclature change would allow for direct comparison of clinical outcomes for lesions along the same DREZC sensory pathway using technology actively utilized in clinical practice today.

Contributing to these similar outcomes, one must consider an important procedural difference between classic surgical DREZ lesions and fluoroscopically guided DREZC lesions. While small radiofrequency electrodes with 1–2 mm active tips are utilized for ablative radiofrequency DREZ surgeries in an effort to minimize the complications (Table 3), larger active tips (ie, 10mm) can safely be used for pulsed radiofrequency procedures as the temperatures are typically maintained at 42°C, which have not been found to be ablative,^{38,54,55,59} but rather, neuromodulatory.^{9,45,59} The larger active tip may provide enough linear anatomic capture to induce broad neuromodulatory changes, potentially modulating multiple components of the dorsal sensory pathway – an important consideration considering the anatomic variability of

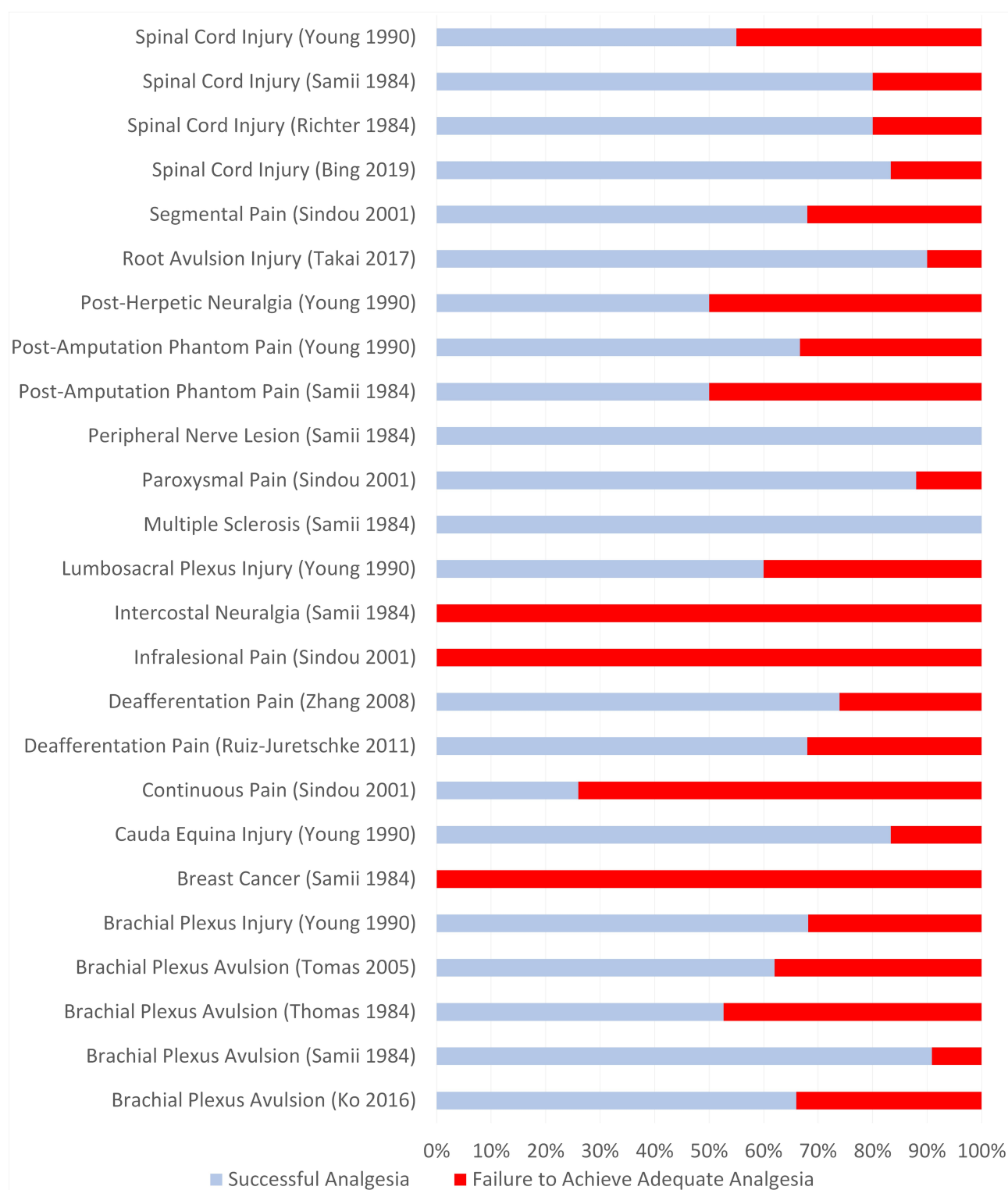


Figure 6 Surgical DREZ RF lesion success and failure rates to achieve adequate analgesia per indication.

DRGs and DRs (Tables 1 and 2), the variability of their locations relative to their respective foramina and DRLs (Figures 2 and 4), and variability in number, size, and location of both DRLs^{2,5,21,24,32–35} and the DREZ,

itself.^{2,5,24,32,34} Even with the anatomical variability of the DRG in relation to the foramen, the efficacy of pulsed radio-frequency lesions was maintained while cannula placement varied along the linear dorsal afferent pathway, indicating

that the cannula tip does not significantly impact efficacy when DREZC neurosensory stimulatory capture is attained.³⁸ Although this may partially be explained due to the larger pulsed radiofrequency active tip capturing a larger anatomic portion of the DREZC, given the anatomic variability of the DRGs, DRs, DRLs, and DREZ, it appears that the neuromodulatory effects can materialize with a pulsed radiofrequency lesion at variable segments of the DREZC.

Thus, the use of the term, “DREZC lesion,” avoids the presumptive incorrect classic segmental nomenclature. If, for example, an T12 fluoroscopically-confirmed intraspinal cannula tip results in appropriate sensory stimulation in a patient who had 2 DRGs, each located extraforaminally, it would be incorrect to label such a procedure as pulsed radiofrequency of the DRG since this would be a lesion of the DRL or DREZ, as evidenced by an intraspinal cannula tip, more proximal to the extraforaminal DRGs. In this scenario, the DRG could not itself be visualized using fluoroscopy thereby limiting the accuracy of the current nomenclature. “DREZC lesion,” on the other hand, would be accurate in same scenario.

Conclusion

The purpose of this translational review was to provide evidence in the support of the natural evolution of the nomenclature of radiofrequency lesions from lesions of individualized components of the dorsal afferent pathway to, henceforth, refer to these neuroablative and/or neuromodulatory radiofrequency lesions of this linear pathway as, “Dorsal Root Entry Zone Complex (DREZC) lesions.” Review of anatomic variability, procedural limitations and complications, along with patient outcomes, all support the change to this more sensitive and inclusive terminology nomenclature. Clinically, and academically, this would be a more accurate nomenclature, whereby technological limitations for intraprocedural identification and differentiation of any one component of the DREZC to another adjacent component could be considered less clinically relevant with the new, more encompassing, nomenclature, given that clinical data show similar outcomes despite these limitations. This review demonstrates that technological limitations for intraprocedural identification and differentiation of any one component of the DREZC to another component could be considered to have limited clinical relevance since lesions of individual components of this linear dorsal sensory pathway (DREZC) have yielded similar clinical outcomes by interrupting signal transmission through the same pathway. Furthermore, to arbitrarily name presumptive individual

component lesions of the DREZC inaccurately would be inappropriate. Clinically, and academically, “DREZC Lesions,” would provide a more inclusive and accurate nomenclature for collective RF lesions of the DREZC components, which can provide a cohesive direction for reporting neuroablative outcomes for DREZC lesions. Future imaging advancements may improve clinical accuracy, at which point the nomenclature may be reassessed yet again, but given today’s limitation, the evidence supports the use of the more sensitive and accurate nomenclature, DREZC lesions.

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Disclosure

Alaa Abd-Elsayed reports serving as a consultant for Medtronic and Avanos. The authors report no other potential conflicts of interest in this body of work.

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