Cancer Pain & Neuromodulation

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Speaker's Disclosure

- *2023.9. – Present.* Tenured Professor at the SNU College of Medicine
  - *2016.9. – 2023. 8.* Associate Professor at SNUH
  - *2011.3. – 2016. 8.* Assistant Professor at SNUH
- *2022. 9. – Present.* Secretary, *CRPS SIG, IASP.*
- *2021. 3. – Present. Board of Exam Officer, FIPP & CIPS, WIP*
- *2018. 9. – Present.* Director, Pain Center at SNUH
- *2016.11. – Present.* Director of International Coop, KPS

Off-Label Product Use

Will you be presenting or referencing off-label or investigational use of a therapeutic product?	
	No
√	**Yes, as follows:** Botulinum toxin for lumbar sympathetic block

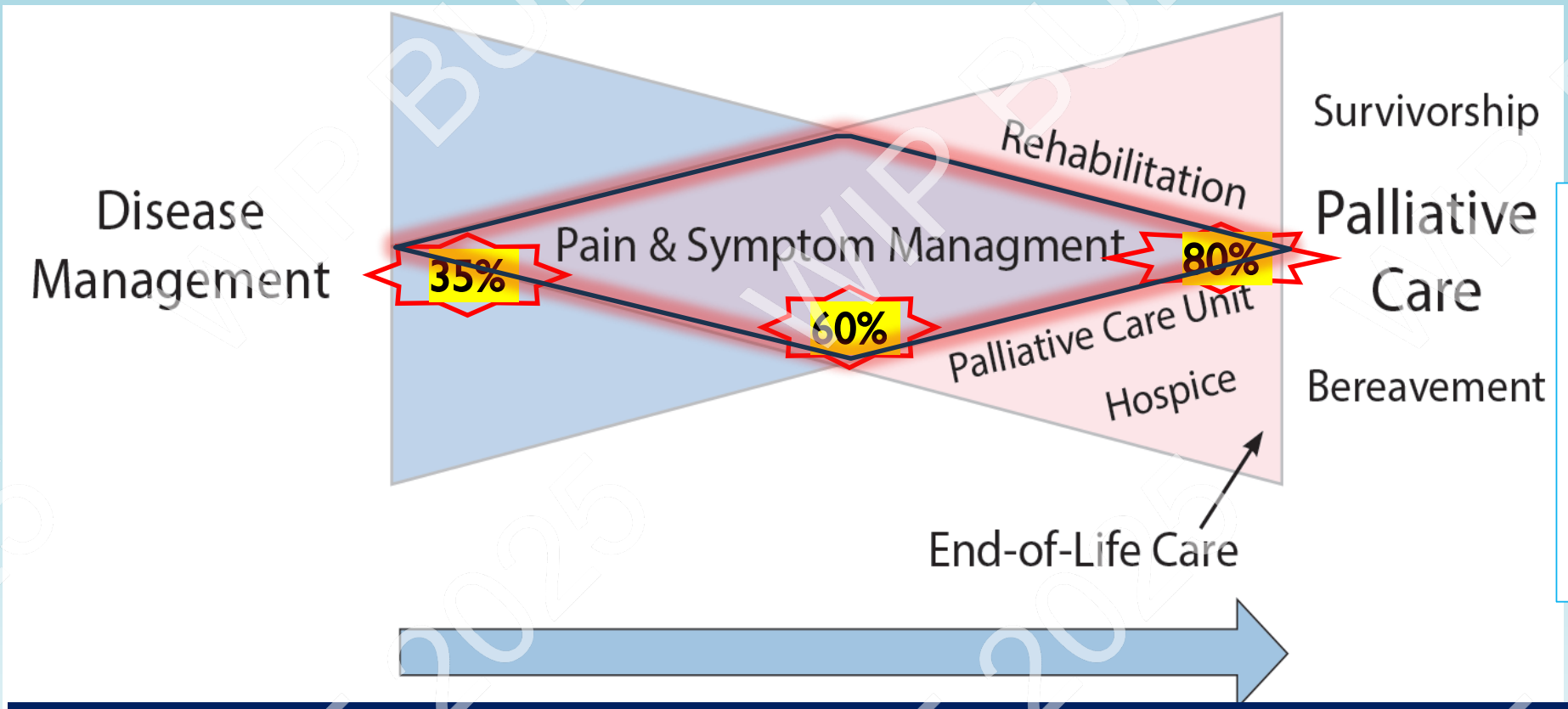
Learning Objectives

Regarding Neuromodulation for Managing ***Cancer Pain***,

By the end of this session, the participants will be able to:

- Understand the Adequate ***Indication and Timing for Neuromodulation*** *in Cancer*
- Learn the Evidence of ***Spinal Cord Stimulation*** *therapy in Cancer*
- Adapt Various ***Alternative Neuromodulation Options*** *in Cancer*

The Bow Tie Model of 21st-century Palliative Care



- The strategies of cancer pain management should be different between hospice care and cancer survivors.

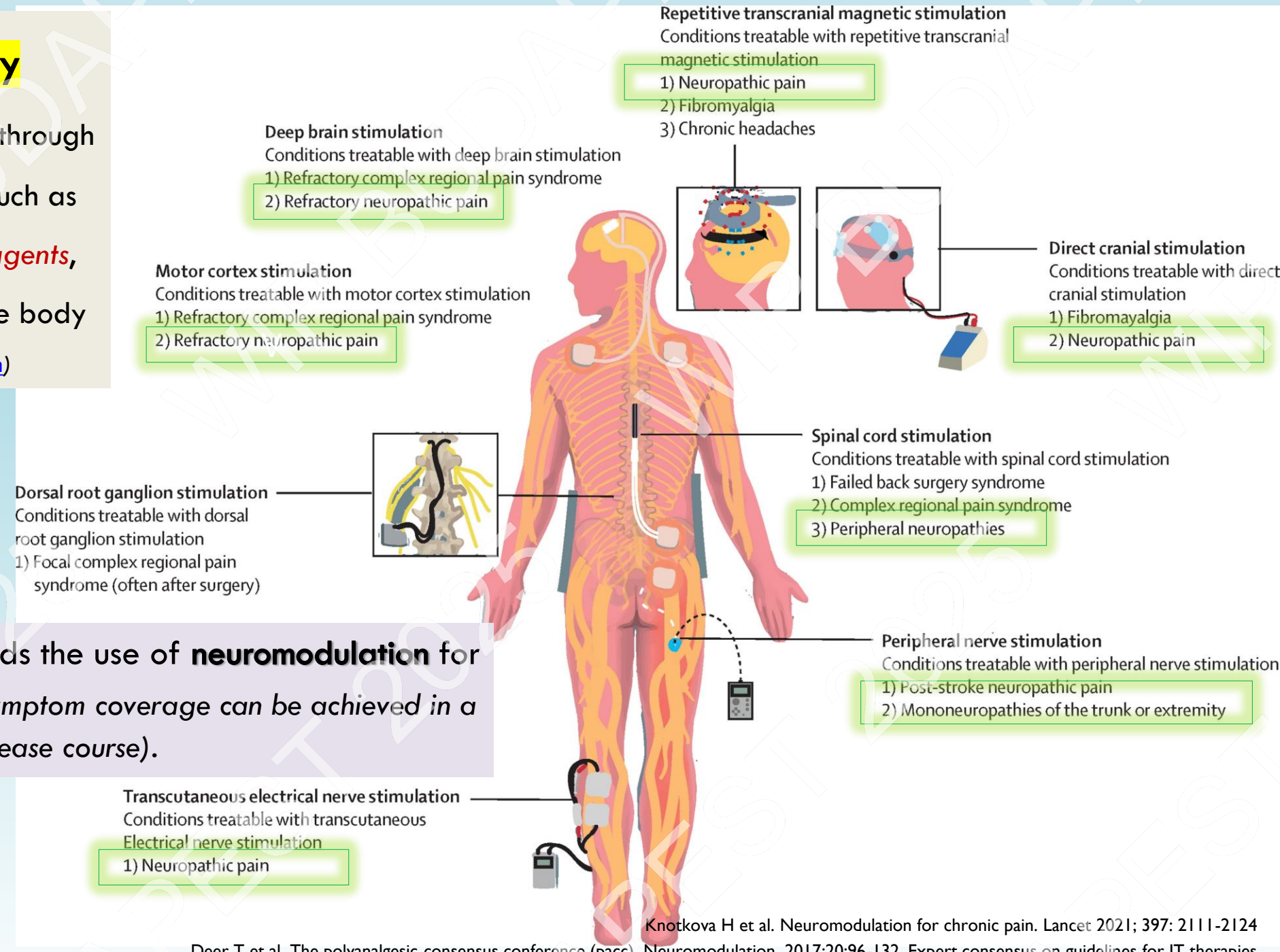
Pain is the most frequent symptom, developing at any stage in Cancer.

Hawley PH . The bow tie model of 21st century palliative care. J Pain Symptom Manage. 2014; 47:e2-5.
Van den Beuken-van Everdingen et al. J Pain Symptom Manage 2016

Neuromodulation Therapy

: The alteration of nerve activity through targeted delivery of a stimulus, such as *electrical stimulation or chemical agents*, to specific neurological sites in the body

(by INS, https://www.neuromodulation.com)



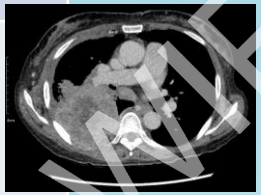
The PACC algorithm recommends the use of **neuromodulation** for **neuropathic cancer pain** *(if symptom coverage can be achieved in a stable disease course)*.

Knotkova H et al. Neuromodulation for chronic pain. Lancet 2021; 397: 2111-2124

Deer T et al. The polyanalgesic consensus conference (pacc). Neuromodulation. 2017;20:96-132. Expert consensus on guidelines for IT therapies

Etiology Neuropathic Pain in Cancer

Etiology	Potential cause
Disease	Infiltration or compression of nerves / Paraneoplastic neuropathies / Bone & epidural meta
Treatment-related	Surgery (post-mastectomy, thoracotomy, amputation) / Radiotherapy Chemotherapy (vinca alkaloids, taxanes, platinum-based agents)
Co-existing condition	Diabetic peripheral neuropathy / Vitamin B deficiency/ Post-herpetic neuralgia / Multiple sclerosis, Trauma, Stroke, etc.



Fallon MT. Neuropathic pain in cancer. British Journal of Anaesthesia. 2013; 111: 105-111.
Roberto A et al (2016) Journal of Pain and Symptom Management; 2016;51: 1091-1102.

Cancer-related NeP accounts for at least *40%* of cancer pain.

- Cancer-related NeP exists in ***50%*** of cancer patients at their first visit to the SNUH Pain Center.
- Mixed type pain + Neuropathic pain = ***75%*** of cancer

Pain type	Cancer Pain (n = 309)
Nociceptive (0–12)	78 (25%)
Mixed (13–18)	*78 (25%)*
Neuropathic (19–38)	*153 (50%)*

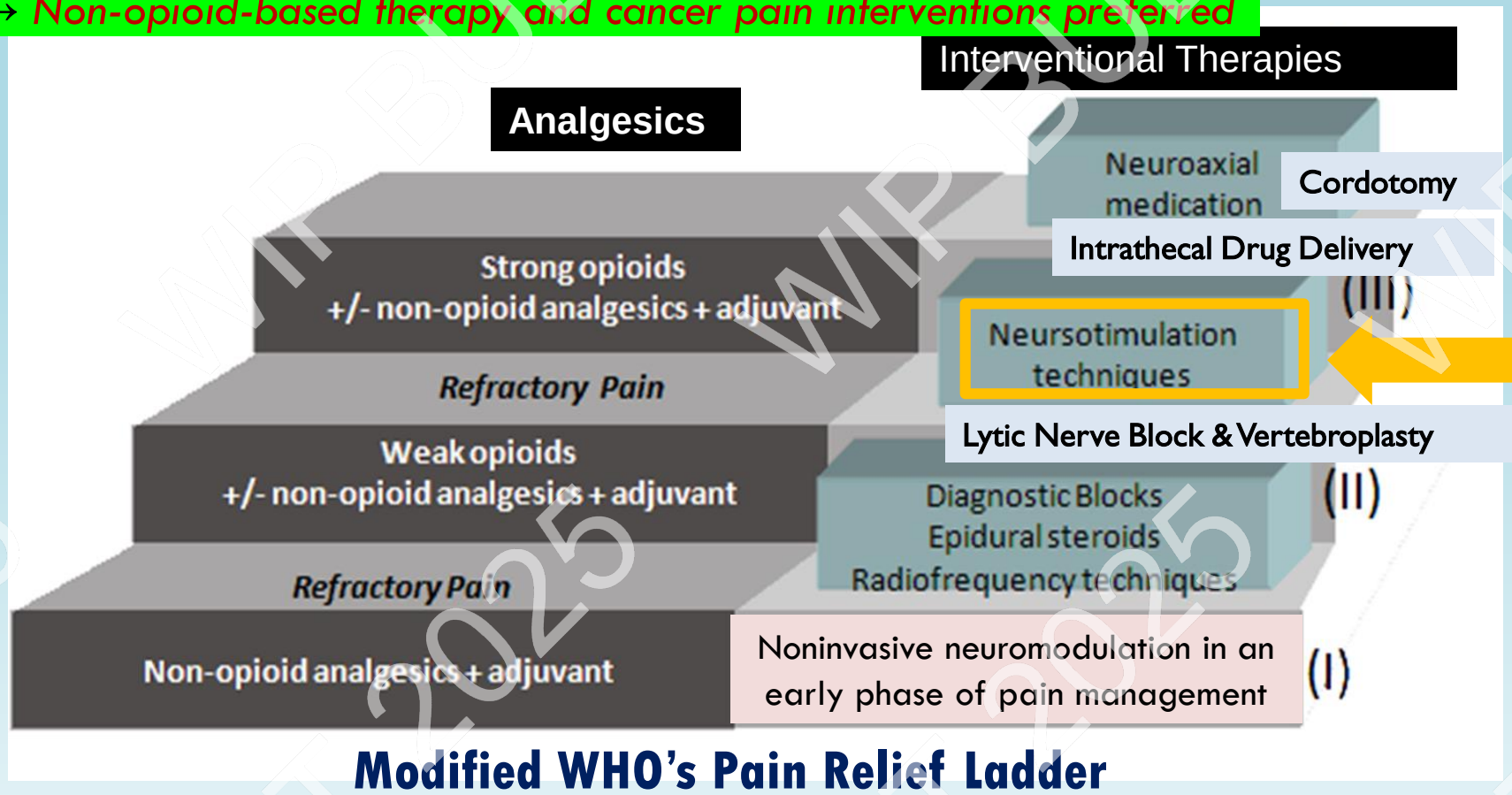
Using the PainDETECT questionnaire

Survey at the SNUH Pain Center in 2019

When is the best timing to consider Neuromodulation therapy?

Associations with long-term opioid use and shorter survival time in cancer

→ *Non-opioid-based therapy and cancer pain interventions preferred*



- Invasive neuromodulation is considered an intermediate option rather than a last-resort option.

- Pain interventions should be considered as an **earlier implementation (step II) in cancer,** providing 1) better pain control, 2) lower opioid consumption, and 3) increased survival time.

1. Boland JW et al. Is regular systemic opioid analgesia associated with shorter survival in adult patients with cancer? A systematic literature review. Pain. 2015;156:2152-63.
2. Amr YM, et al. Neurolytic sympathectomy in the management of cancer pain-time effect: a prospective, randomized multicenter study. *J Pain Symptom Manage.* 2014;48:944-52
3. Dobosz L, et al. Invasive treatment of pain associated with pancreatic cancer on different levels of WHO analgesic ladder. *BMC Surg.* 2016;16:20

Learning Objectives

Regarding Neuromodulation for Managing ***Cancer Pain***,

By the end of this session, the participants will be able to:

- Understand the Adequate ***Indication and Timing for Neuromodulation*** *in Cancer* Pain
  - Neuromodulation is effectively adapted to *cancer-related neuropathic pain*, and recommended *before taking strong opioid medication*, especially in patients with *survivorship.*

- Learn the Evidence of ***Spinal Cord Stimulation Therapy*** *in Cancer* Pain
- Be able to Adapt Various ***Alternative Neuromodulation Options*** *in Cancer* Pain Management.

SCS for Cancer Pain (Case reports & Retrospective case reviews)

Author, Y	Study Type (N)	Cancer type	Pain Etiology	Stimulation mode	Results	F/U (m)
Eisenberg, 2002	Case report (n = 1)	Meningioma	Cancer-related UE & LE	Tonic single lead	*NRS 10→ 1.5, Improved QoL, Reduced opioid*	1
Cata, 2004	Case series (n = 2)	Melanoma, Ewing sarcoma	*Treatment-related* LE	Tonic dual lead	NRS 4-6→ 1-3, Improved QoL, Reduced opioid	3-4
Ting, 2007	Case report (n = 1)	Pancreatic Meta Ca	*Treatment-related* LE	Tonic dual lead	Pain relief at 1m & improved QoL	1
Hamid, 2007	Case report (n = 1)	Lung Ca spinal meta	*Treatment-related* LE	Tonic single lead	NRS 10→ 0.5, Improved QoL, Reduced opioid	18
Yakovlev, 2008	Case series (n = 2)	Colon Ca Anal Ca	*Treatment-related* & Cancer-related LE	Tonic dual lead	NRS 7-8→ 1-1.5, Improved QoL	12
Lee, 2009	Case report (n = 1)	Spinal meningioma	*Treatment-related* LE	Tonic dual lead	NRS 9→ 1, Improved QoL, Reduced opioid	2
Yakovlev, 2010	***Retrospective case review*** *(n = 14)*	Lung Ca	*Treatment-related* chest & UE	Tonic dual lead	NRS 7.4→ 3.7, Improved QoL, Reduced opioid	12
Viswanathan, 2010	Case series (n = 4)	Chondrosarcoma, MSK Ca	*Treatment-related* LE & back	Tonic dual lead	Improved QoL, Reduced opioid	29
Nouri, 2011	Case report (n = 1)	Prostate Ca	Cancer-related testicular pain	Tonic dual lead	NRS 5 → 1, Improved QoL, Reduced opioid	1.5

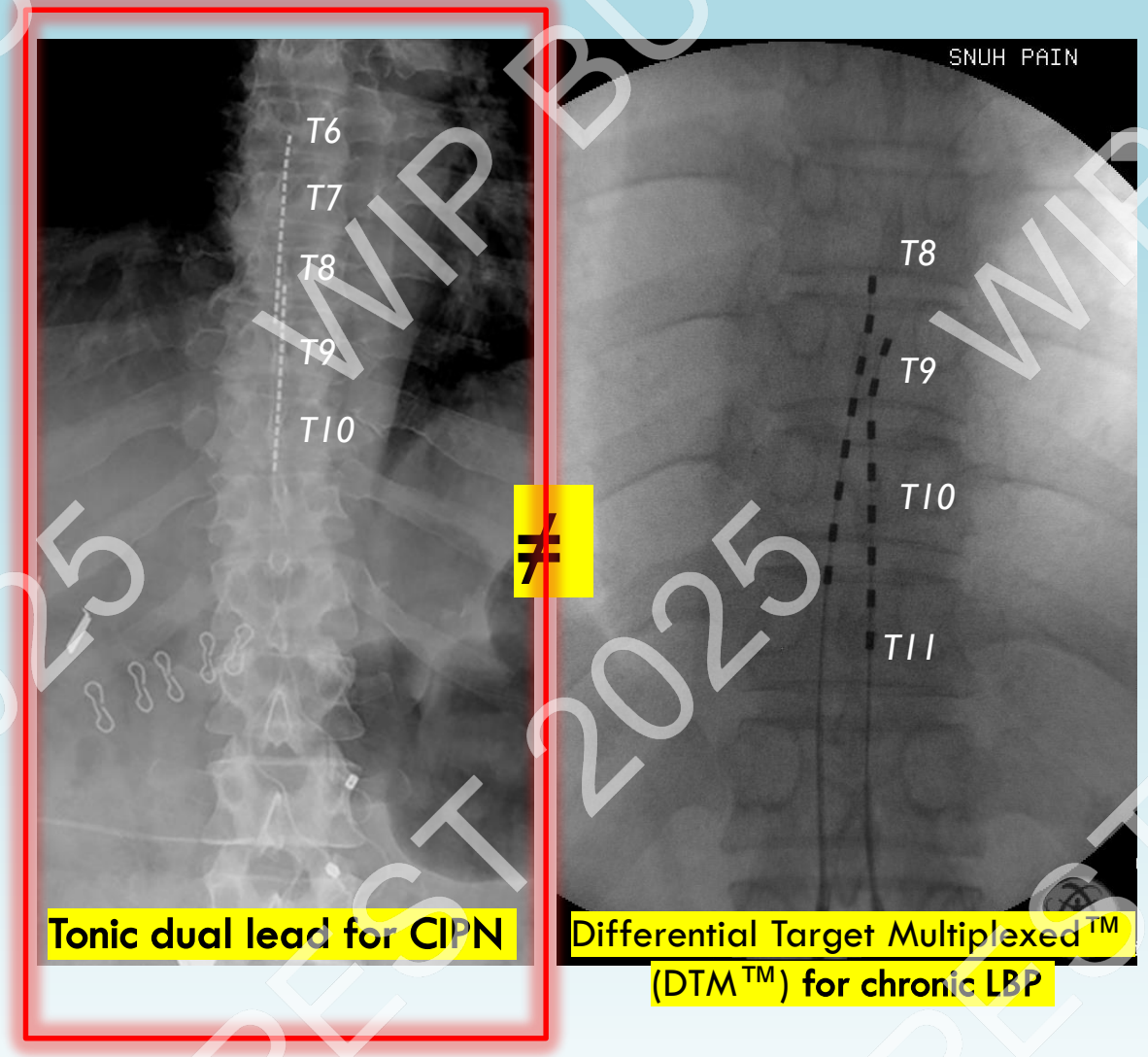
Author, Year	Study Type	Cancer	Etiology	Mode	Results	F/U(m)
Yakovlev, 2012	***Retrospective*** (n = 15)	Colon Ca Meta	*Treatment-related* LBP & LE	Tonic dual lead	NRS 7→ 2.6, Improved QoL, Reduced opioid overall	12
Wininger, 2012	Case report (n = 1)	Lung Ca	*Treatment-related(CTx); UE*	Tonic dual lead	NRS 8.5→ 1.5, Improved QoL, Reduced opioid	24
Elahi, 2013	Case report (n = 1)	Prostate Ca	*Treatment-related* Pelvic & LE	Tonic dual lead	NRS 8.5→ 1.5, Improved QoL, Reduced opioid	10
Mirpuri, 2015	Case report (n = 1)	Osteochondroma	Cancer-related LE	Tonic paddle lead	70-80% pain reduction, Improved QoL, Reduced opioid	6
Ab 20						24
Hutson, 2017	Case report (n = 1)	Thyroid Ca meta to sacrum	Cancer-related LBP & LE	Tonic dual lead	Improved QoL, Reduced opioid	None
Maeda, 2020	Case report (n = 1)	Lung Ca	*Treatment-related(CTx)* chest & UE	Tonic dual lead	NRS 8→ 4, Improved QoL, Reduced opioid	8
Quintero-Carreno, 2021	Case report (n = 1)	MSK Ca	*Treatment-related* UE & LE	Tonic dual lead	NRS 9→ 2, Improved QoL, Reduced opioid	3
Chung, 2021	***Retrospective case review*** (n = 7)	Breast Ca	*Treatment-related(CTx)* UE	Tonic dual lead	NRS 8.6→ 4.2, Improved QoL overall, Reduced opioid overall	22.2

SCS efficacy may be a therapeutic option for managing *chemotherapy-related neuropathic pain*

SCS for Chemotherapy-induced Peripheral Neuropathy

- **Chemotherapy-induced peripheral neuropathy**
  - Occurs in ~ 40% treated with platinum-containing compounds, vinca alkaloids, and Taxol agents
  - Common reasons for discontinuation of chemotherapy
  - In survivors, pain and motor dysfunction increase morbidity and healthcare expenditures.

- **SCS therapy in Cancer patients**
  - Conventional tonic SCS (dual-lead multiplex ***from T5 to T10***) could be a therapeutic option, but some patients could poorly tolerate paresthesia.
  - Paresthesia-free (Burst stimulation, high-frequency, closed-loop; accelerometry or ECAP) or ***DRG stimulation*** has not yet been reported in cancer.



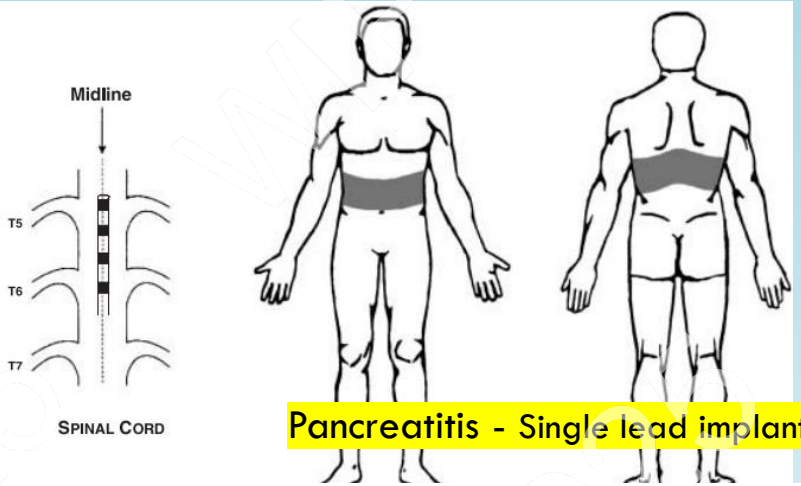
Sheldon BL et al. Front. Pain Res. 2021; 2:699993

Neuromodulation. 2005 Jan;8(1):14-27. doi: 10.1111/j.1094-7159.2005.05216.x.

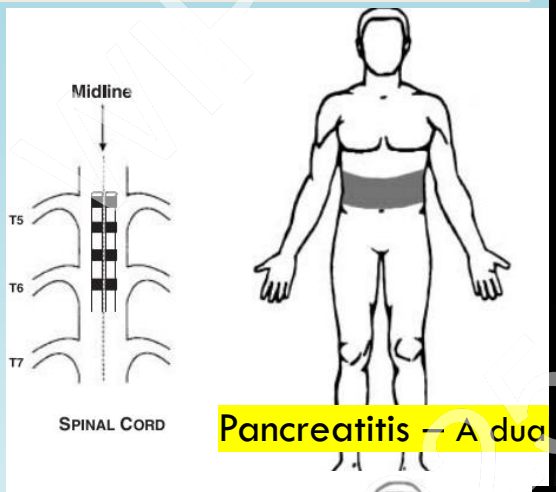
Application of spinal cord stimulation for the treatment of abdominal visceral pain syndromes: case reports

Yasin N Khan [1], Shariq S Raza, Elizabeth A Khan

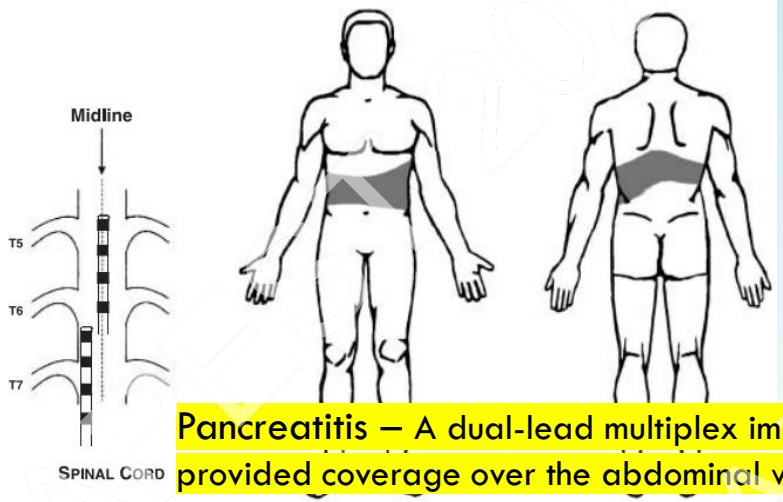
Leads were located from *the mid-T(T5-T6)* to *the lower-T(T9-T10)* in 9 patients.



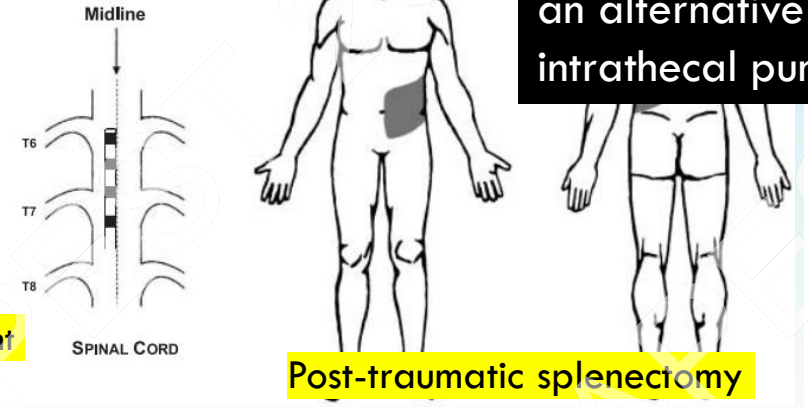
Pancreatitis - Single lead implant



Pancreatitis – A dua



Pancreatitis – A dual-lead multiplex implant provided coverage over the abdominal wall



Post-traumatic splenectomy

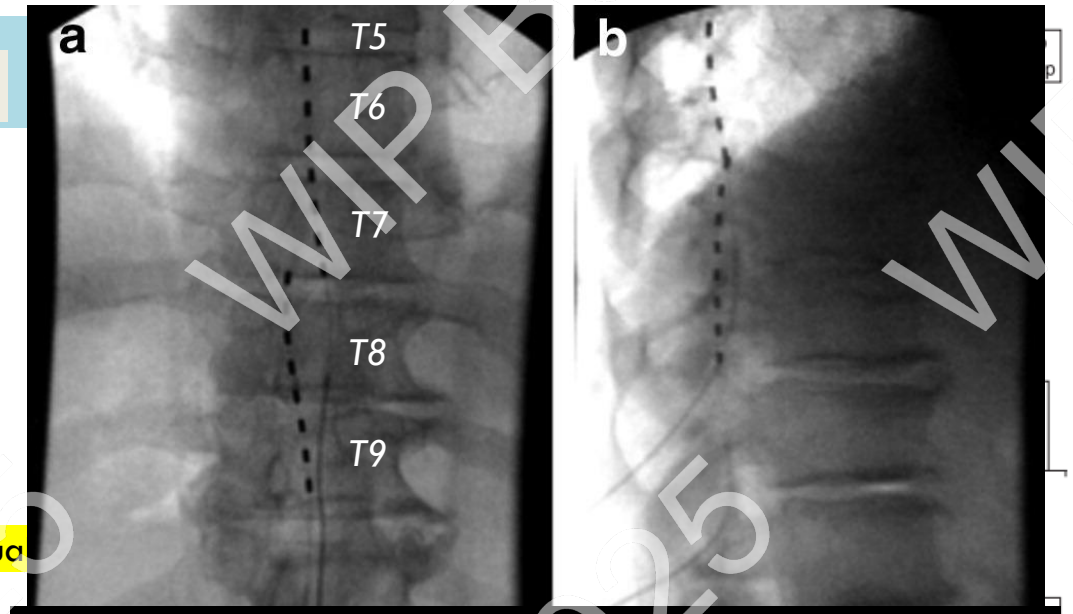
Journal of Palliative Medicine > Vol. 21, No. 8

Research Article | FULL ACCESS | Published Online: 1 August 2018

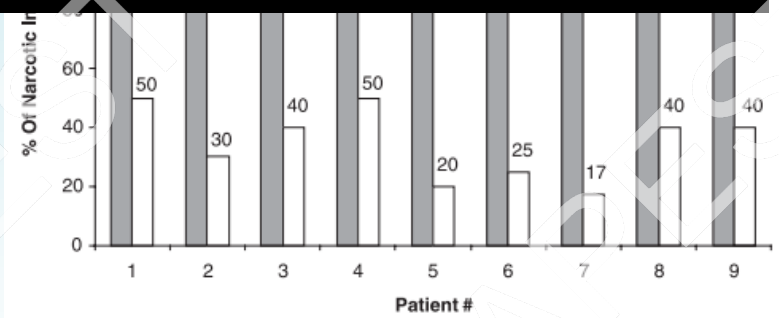
Neuromodulation and Pancreatic Cancer Pain

Authors: Mary So, Nitin Bansal, and Mohammad M. Piracha | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Palliative Medicine • https://doi.org/10.1089/jpm.2018.0109



SCS in pancreatic cancer-related abdominal pain is an alternative option to traditional neurolysis, intrathecal pump, and oral analgesics.



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- Learn the Evidence of ***Spinal Cord Stimulation Therapy*** *in* Cancer Pain
- Adapt Various ***Alternative Neuromodulation Options*** *in* Cancer Pain
  - Pain Scrambler therapy
  - Botulinum toxin injection at the sympathetic ganglia

Pain Scrambler Therapy

Moon JY et al. Clin J Pain. 2016; 57:475-81

ORIGINAL ARTICLE

Predictive Factors Associated With Success and Failure for Calmare (Scrambler) Therapy

A Multicenter Analysis

Jee Youn Moon, MD, PhD, Connie Kurihara, RN,† Judith P. Beckles, RN,† Karen E. Williams, RN,‡ David E. Jamison, MD,† and Steven P. Cohen, MD§‖*

- Noninvasive neuromodulation by *Scrambling* the pain signal pathway with 5 artificial neurons
- 10 consecutive sessions are usually necessary

- N = 147 (from 3 hospitals: Walter Reed, Naval Hospital -Camp Lejeune, SNUH)
- The success rate was ***38.1%*** (> 50% pain relief for >

Neuropathic pain results in a positive treatment outcome of Pain Scrambler Therapy

- ***Neuropathic*** (OR 24.8, 95% CI 2.5 – 248.9; p< 0.01) or ***Mixed*** (OR 10.5, 95% CI 1.1 – 101.3; p=0.04) pain were positive factors.

European Journal of Oncology Nursing 21 (2016) 1–7

Contents lists available at ScienceDirect

European Journal of Oncology Nursing

journal homepage: www.elsevier.com/locate/ejon

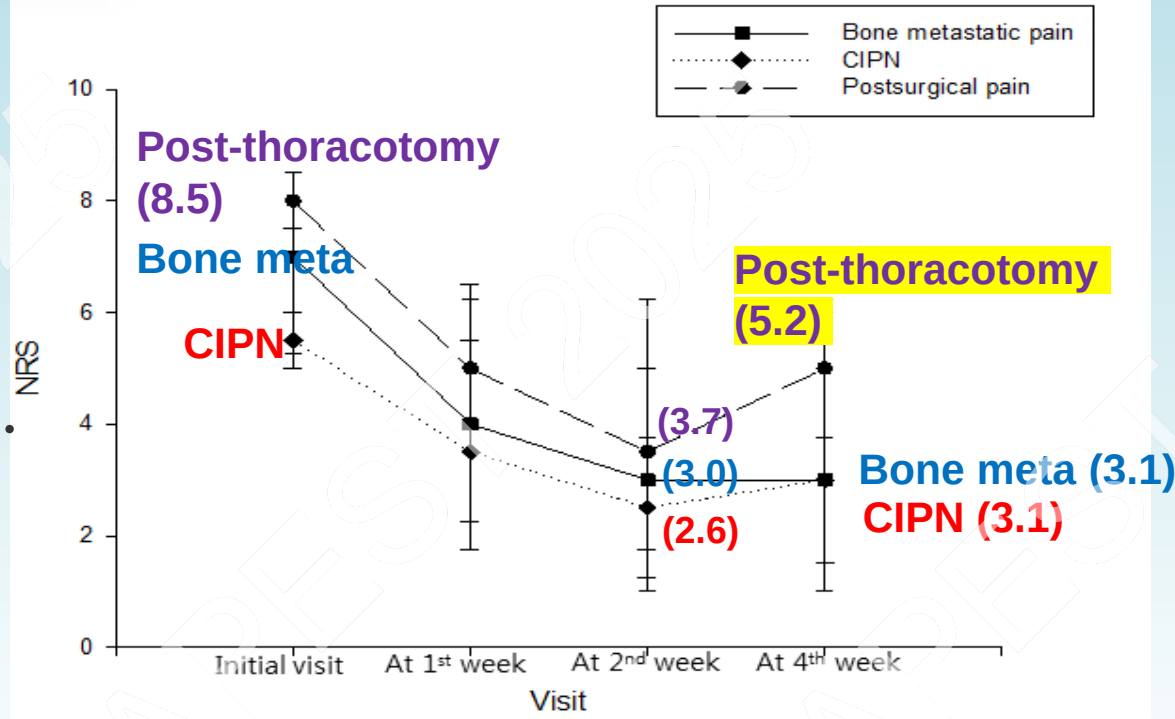
An exploratory study on the effectiveness of "Calmare therapy" in patients with cancer-related neuropathic pain: A pilot study

Sang Chul Lee [a, 1], Keun Suk Park [a, 1], Jee Youn Moon [a, *], Eun Jung Kim [a], Yong-Chul Kim [a], Hyejin Seo [a], Joon Kyung Sung [a], Da Jeong Lee [b]

[a] Department of Anesthesiology and Pain Medicine, Seoul National University Hospital College of Medicine, Seoul, Republic of Korea
[b] University Medical Center, De La Salle Health Sciences Institute, Dasmariñas, Cavite, Philippines

Moon JY et al. Eup J Onc Nur. 2016; 21:1-7

- A prospective pilot study (10 consecutive therapies)
- N = 20 [CIPN (n = 6), bone metastatic nerve compression (n = 7), and *post-thoracotomy pain* (n = 7)]
- NRS pain scores were reduced from 7.4 to 3.7 at 1m.
- Rescue opioid consumption decreased at 1m (p = 0.050)



Pain Scrambler Therapy in Children

Pediatric Blood & Cancer

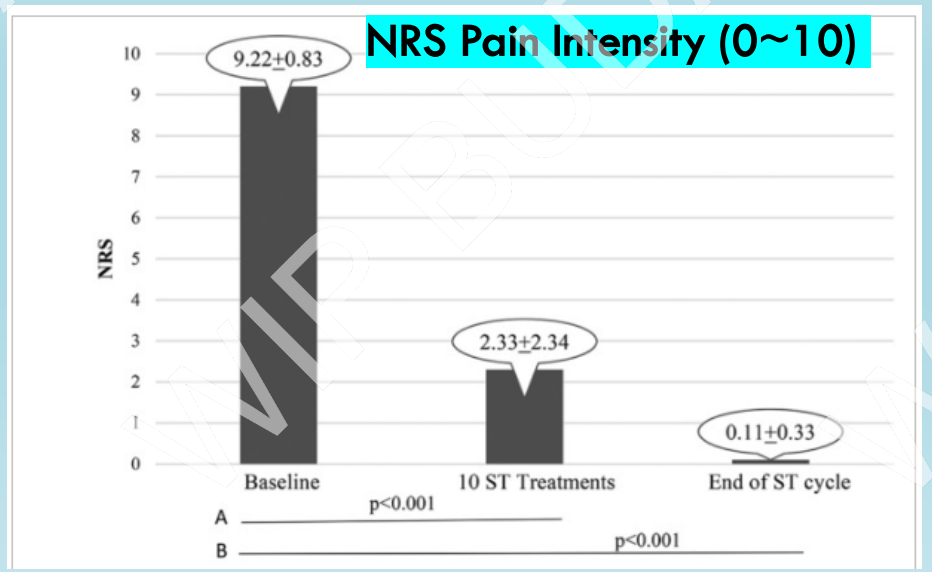
RESEARCH ARTICLE | Full Access

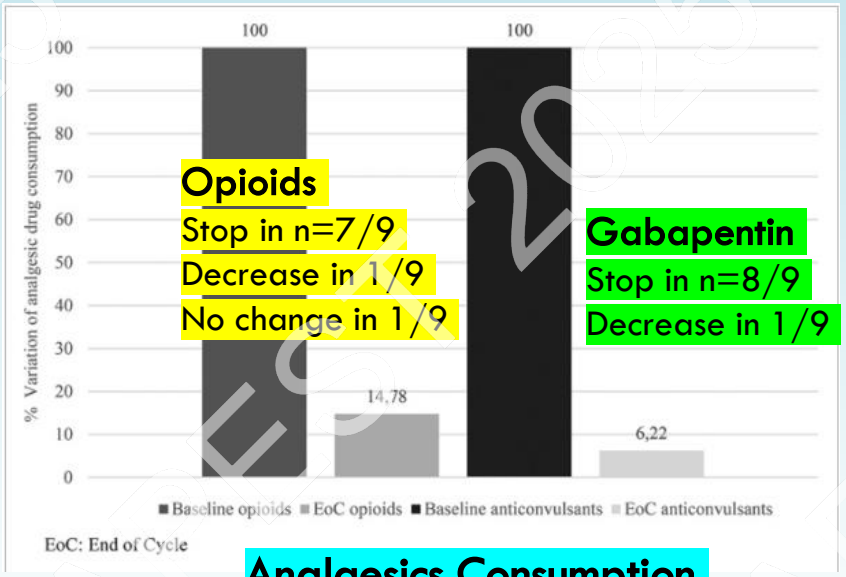
Scrambler therapy efficacy and safety for neuropathic pain correlated with chemotherapy-induced peripheral neuropathy in adolescents: A preliminary study

Caterina Tomasello, Rita Maria Pinto, Chiara Mennini, Elena Conicella, Francesca Stoppa, Umberto Raucci

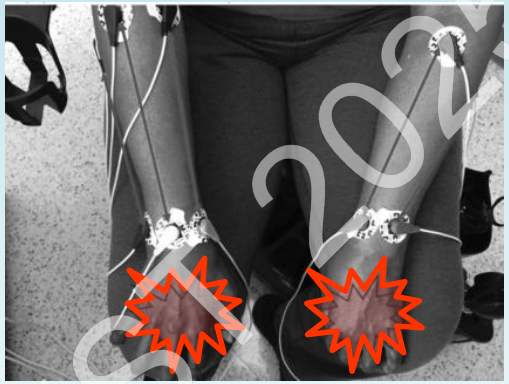
First published: 06 April 2018 | https://doi.org/10.1002/pbc.27064 | Citations: 26

- N = 9 (age: 12~17 yrs) with ALL, AML, APL, HD, NB
- Start of ST to the onset of CIPN = 22~ 58 days
- ST days = 8~21 sessions

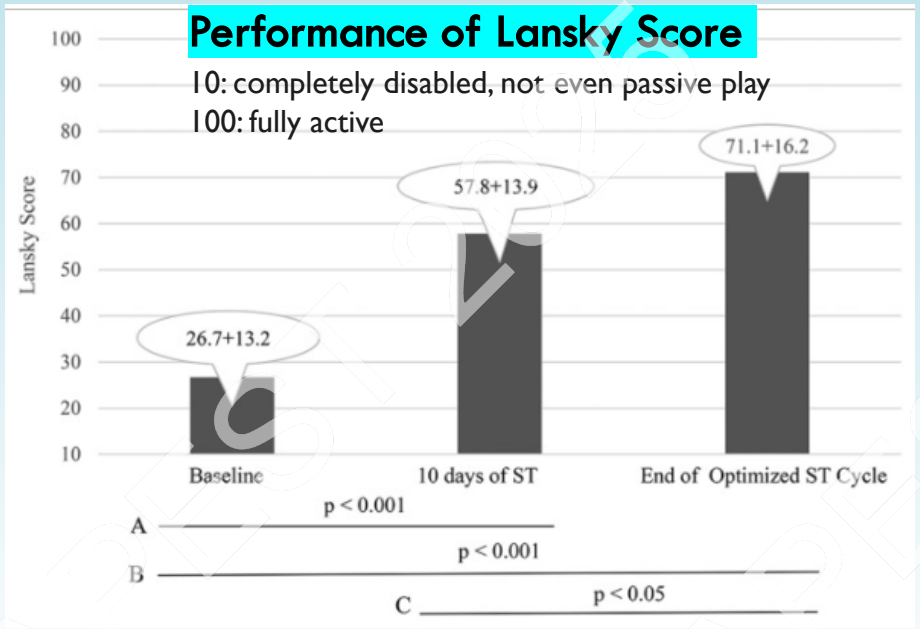




Analgesics Consumption

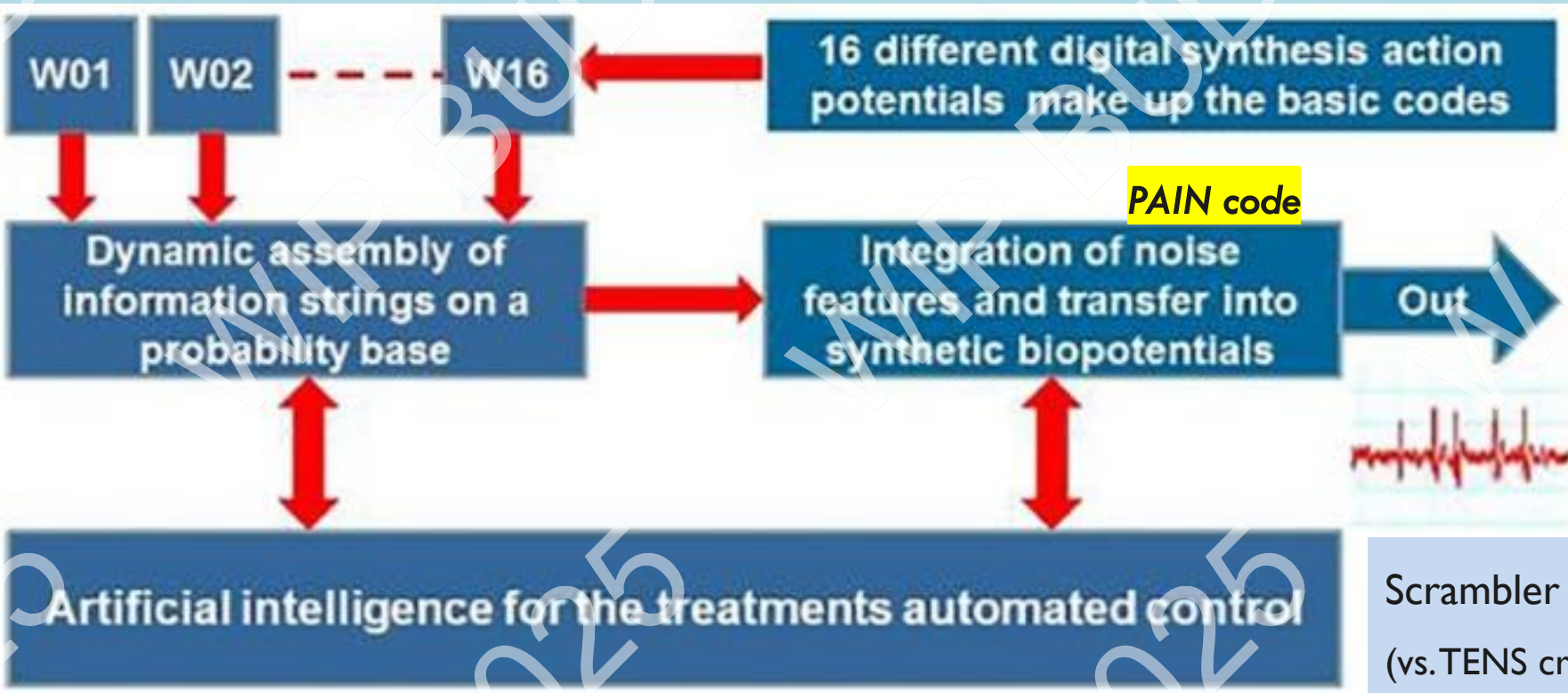


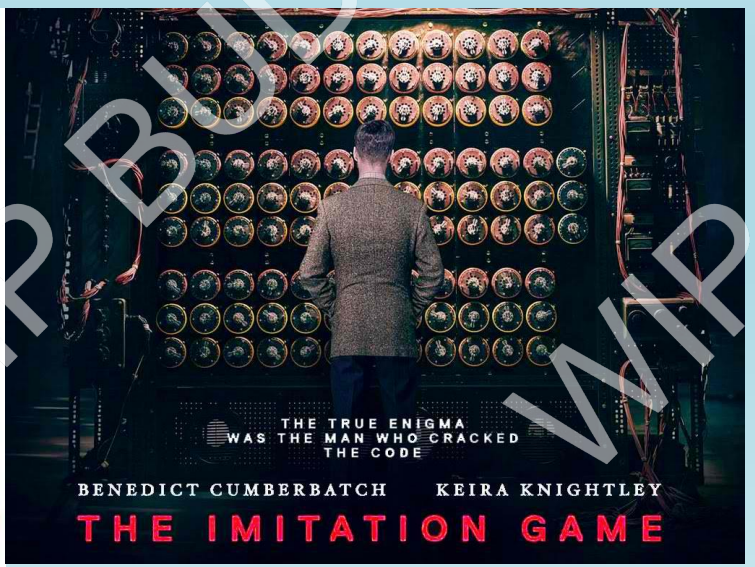
J Palliat Med 2021:24:1579-81



Scrambler Therapy: the Mechanism

Is it an Enigma device?





Scrambler therapy ~ 5.5 mA

(vs. TENS creates linear pulses with 30-150 mA, interacting with A-delta fibers.

- *5* artificial neurons interact with surface ***C-fibers***.
- It creates *16 different synthetic action potentials*, followed by dynamic assembly and modulations, finally developing *256 (16x16) information strings* (no pain messages).
- "Noise" is integrated into the main information strings to make the emission of the ST.

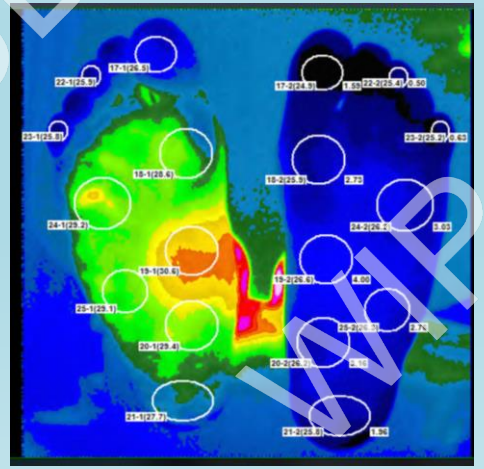
PAIN code

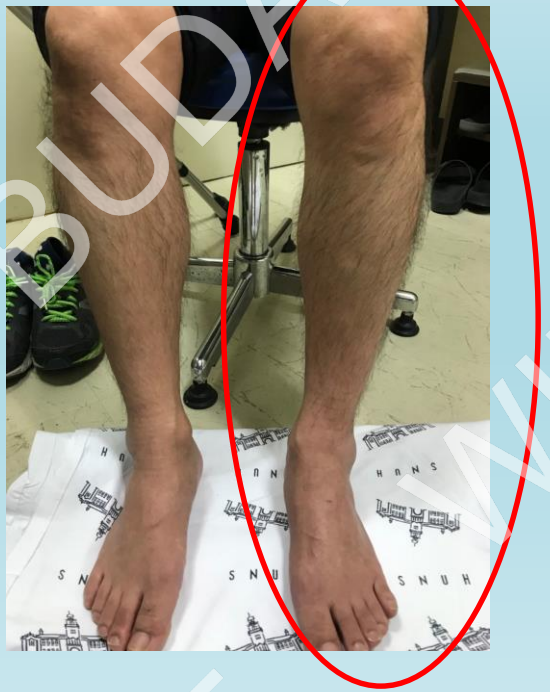
M Giuseppe. Integr Cancer Ther. 2019; 18:1534735419845143

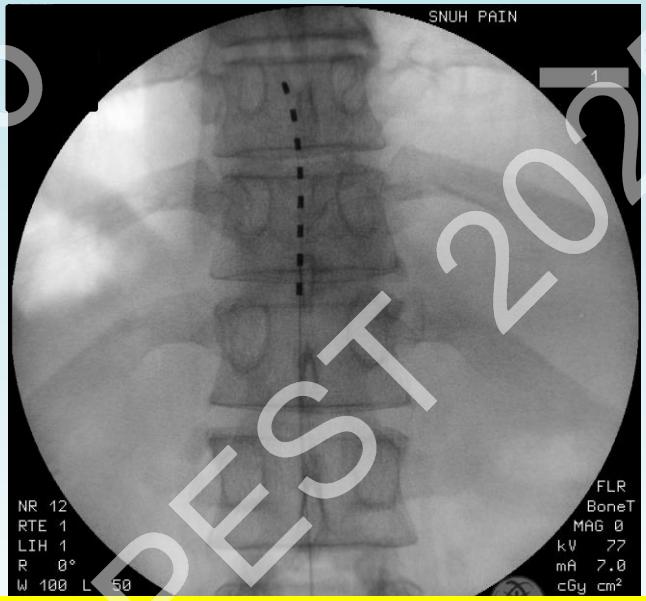
Botulinum Toxin for LSGB in Cancer

M/54 SOO (175 cm / 75 kg)

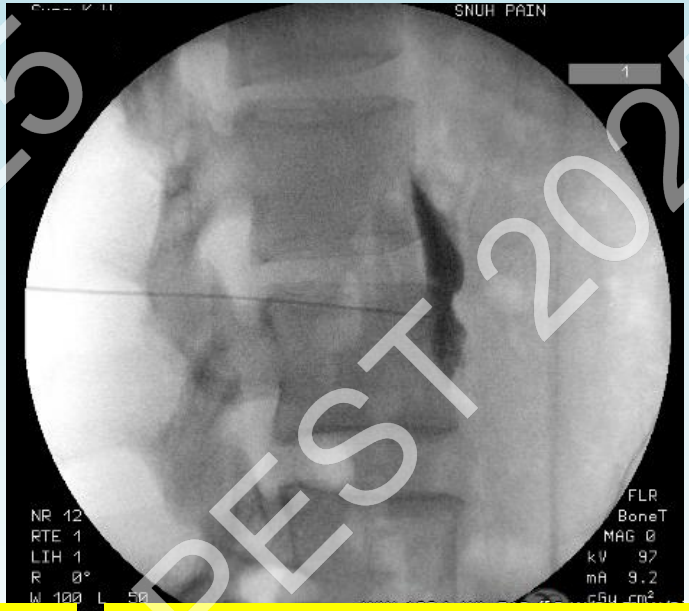
- Rectal malignancy removal *(Cancer Survivor)*
- Lt sciatic nerve injury after cancer removal
- Mimicking CRPS type II
- Small fiber neuropathy after chemotherapy (platinum-based)
- Oral Med (anti-convulsant / anti-depressant/opioids)
- NRS: 7/10 (average), 9/10 (Breakthrough-like)







SCS trial and implantation (tonic type)



LSGB with BTx type A 100u at the L2 (50u) & L3 (50u)

NRS 3/10 with opioid med as prn

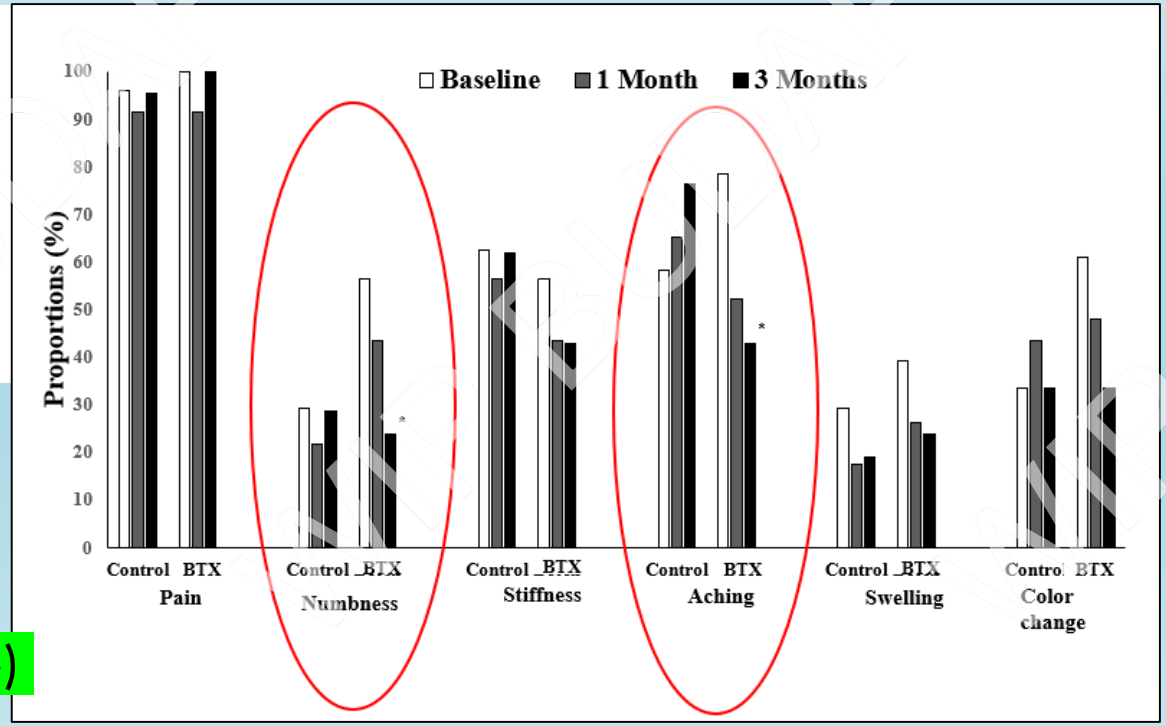
- SCS improves background pain
- LSGB with BTx (75-100u) every 3-4 months reduced # of tremor and paroxysmal pain attacks.

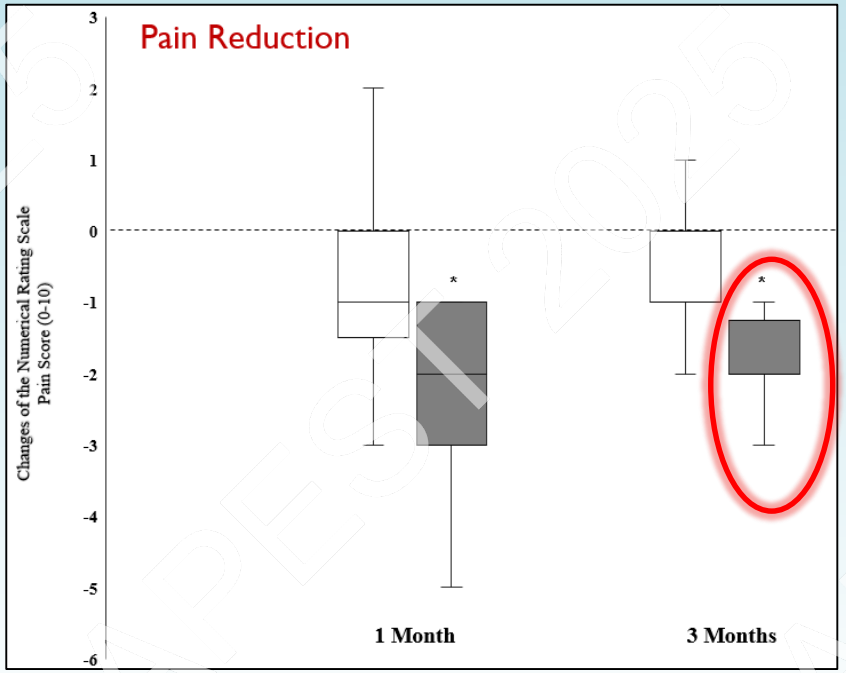
Randomized Controlled Trial > Anesthesiology. 2022 Feb 1;136(2):314-325.
doi: 10.1097/ALN.0000000000004084.

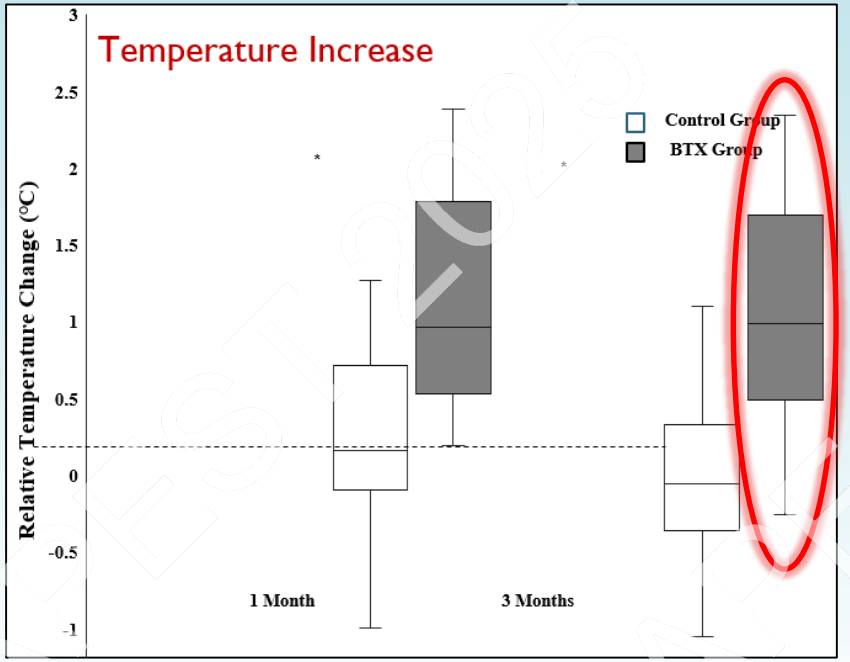
Botulinum Toxin Type A for Lumbar Sympathetic Ganglion Block in Complex Regional Pain Syndrome: A Randomized Trial

- N = 48 CRPS patients (24 in BTX vs. 24 in LA only)
- Pain duration (25 months [SD 10])

BoNT-A improved pain intensity, temperature discrepancies, and aching pain for 3 months (vs. LDC alone)







No severe adverse events in botulinum toxin injection.

The relatively long duration of a single injection of botulinum toxin on sympathetic ganglia could be an example of chemical neuromodulation.

Take-Home Messages

- **Indication and Timing for Neuromodulation** in Cancer Pain Management
  - Cancer survivor vs. Cancer hospice / Pain characteristics (**Neuropathic pain**)
  - Starting strong opioid medication
- **Spinal Cord Stimulation Therapy** in Cancer Pain Management
  - Effective for CIPN: Large-scale RCTs have not been performed.
- **Alternative Neuromodulation Options** in Cancer Pain Management
  - Pain Scrambler therapy and BTx type A for sympathetic blocks

Cancer pain is a unique experience for every cancer patient.
Treatment plans need to be individually tailored to address this.

Thank you for your time!

Questions?

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snu23802@snu.ac.kr