# Comparison between Dorsal Root Ganglion Thermal Radiofrequency versus Pulsed Radiofrequency for the Management of Intractable Metastatic Pain in Thoracic Vertebral Body

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# INTRODUCTION

Metastatic disease to the bone has been a crippling devastating complication of various cancers, with unbearable pain [1]. Knowledge surrounding the pathophysiology of painful osseous metastases is rapidly changing [2]. Metastatic bone pain is characteristic of cancer pain and is a form of refractory cancer pain, as the pain includes not only nociceptive but also neuropathic pain that induces a peripheral and central sensitization.

The development of medication dose-limiting side effects, limits analgesic efficacy in nearly 42% of cancer pain patients [3].

In recent years the use of pulsed radiofrequency (PRF) to treat chronic pain conditions has generated intense interest in the pain community [4]. PRF is a minimally invasive, target-selective technique that has reported benefit at reducing post-amputation stump pain, chronic radicular/ganglion pain , neuropathic pain , and arthropathic pain [5,6].

In **2008**, **Zeldin** and **Ioscovich** published 3 cases of patients who suffered from uncontrolled vertebral/paravertebral metastatic pain and were successfully treated by fluoroscopically

guided selective dorsal root ganglion ( DRG) PRF (PMG-230 Baylis Medical com. Inc. Canada) [7]. They concluded that that PRF on selective DRG bilaterally under fluoroscopic guidance in patients with pain secondary to metastasis in the Thoracic vertebral body and who were unsuccessfully treated with opioids, may offer new opportunities for metastatic pain treatment and encourage future studies.

Another case series which was conducted by **Young-Chang P. Arai et al.,** in **2015** has concluded that DRG pulsed RF procedure provided sound pain relief for patients with intractable vertebral metastatic pain. PRF on DRG procedure provided sound pain relief for patients with intractable vertebral metastatic pain [8].Studies using animal models have clarified the anti-nociceptive effects of PRF on the DRG, it induces inhibition of excitatory c-fiber responses and a global reduction of evoked synaptic activity [9,10]. Several authors have reported that the anti-nociceptive actions induced by PRF would be due to the enhancement of noradrenergic and serotonergic descending pain inhibitory pathways and the inhibition of excitatory c-fibers [11]. It was found that the application of PRF to a DRG elicits the expression of c-fos in the dorsal horn [12]. The importance of this finding for the clinical effect of PRF is still a subject of discussion. C-fos is a specific marker indicating cellular activity[13].

The alternative of modulation is clearly ablation, and in the vacuum that had persisted this possibility came up. The clinical effect of continuous radiofrequency treatment may therefore reflect a balance between analgesia produced by deafferentation-induced reduction in nociceptive input to the central nervous system and stimulation of pro-inflammatory, pro-nociceptive glial activation in the central nervous system as a consequence of deafferentation. Clinical experience indicates that analgesia is more commonly the result; however, central immune-mediated inflammation may predominate in patients who experience an increase in pain following the procedure [14]. Thermal Radiofrequency (TRF) of the DRG was suggested as an alternative to ganglionectomy to destroy the primary afferents' soma. There is robust literature surrounding RF strategies to treat chronic pain, including treatment of the DRG. TRF uses high frequency electrical current, creating ionic oscillation of the tissue and frictional dissipation of the ionic current, producing heat [15].

Three prospective controlled trials have examined TRF-DRG for treating neuropathic pain stemming from cervical DRG. Van Kleef et al., 1996, Slappendel et al. , 1997 and Haspeslagh et al. , 2006. **Van Kleef et al.** performed a randomized, sham controlled, double blind study with cervicobrachialgia unresponsive to conventional therapy of 12 months duration and response to diagnostic selective nerve root blocks. In a double-blinded fashion, subjects were randomization to the RF group with conventional lesioning of the DRG at $67^0$C for 60 seconds versus no lesioning in the control group. At 8 weeks post operation, eight out of nine RF patients reported success, while two of 11 in the control group, defined as greater than 2- point reduction on the visual analog scale (VAS). This suggested short-term success where dysthesia and hypoesthesia side effects were short lived (lasting <3 months).

There have been no prospective controlled trials on TRF of the thoracic DRG. **Stolker et al.** (Stolker et al., 1994) conducted a prospective uncontrolled trial using TRF of the thoracic DRG at 67 ºC to treat 45 patients afflicted with thoracic segmental pain. They reported that 91% patients obtained > 50% pain relief at 2 months and that 78% continued to experience pain relief for 13 to 46 months. A smaller number of patients (13.3%) reported a transient burning pain in the corresponding dermatome that subsided within 3 weeks. In Neuropathic Pain their review, Malik and Benzon (Malik & Benzon, 2008) concluded that larger-scale, longer term, controlled clinical trials are required to clearly establish the efficacy of TRF-DRG for different types of neuropathic pain, particularly pain originating from thoracic DRG[16]. Although prospective observational and retrospective studies have yielded consistent support for DRG treatment in the cervical, thoracic, lumbar, and sacral regions , controlled studies are less compelling, complicated by the challenge of the lurking deafferentated pain potential. Further, patient selection appears to be vague in predicting treatment outcomes. Larger, sham-controlled, prospective studies are required to elucidate the place of TRF treatment of the DRG for treatment of chronic pain.

# AIM OF THE WORK

To evaluate the effectiveness and safety of Pulsed and Thermal Radiofrequency lesion of the dorsal root ganglion (RF-DRG) on a consecutive group of patients presenting with chronic thoracic pain due to vertebral bone metastasis.

# STUDY DESIGN

This is a Prospective Randomized Controlled trial that will be conducted at the National Cancer Institute. All patients who are eligible for the study will be included and randomized into 3 equal groups.

# PATIENTS AND METHODS

After approval from the Ethics Committee at the National Cancer Institute, Cairo University, and obtaining written informed consent, eighty-one patients with thoracic segmental pain due to metastasis, unresponsive to conventional therapy and meeting the inclusion criteria will be randomly assigned to either one of the two types of treatment, PRF or TRF lesioning of the DRG or the control group. Patients will be carefully evaluated for neurologic deficits and side effects. Assessment of pain will be done at baseline then at 1, 3, 6 months after the procedure. Randomization will be done using randomized permuted block design. Randomization list will be generated through random.org online site.

## INCLUSION CRITERIA:

1. A greater than 6-month history of segmental pain of thoracic vertebral body metastasis origin.

2. Unsatisfactory pain control with oral pharmacotherapy including strong opioid with VAS >5 .
3. Absence of a chronic or progressive motor deficit.
4. Absence of significant sensory deficit.
5. No indication for percutaneous or open surgical intervention.
6. Magnetic resonance imaging and Computed Tomogrophy evidence of thoracic involvement.
7. ASA status of II to III .
8. Age ≥ 18 .
9. Body mass index (BMI) :less than forty and more than twenty .
10. Informed consent

## EXCLUSION CRITERIA:

1. Known sensitivity or contraindication to injected materials: local anesthetics.
2. History of psychological disorders.
3. Evidence of significant neurological deficit.
4. Inability to lie prone.
5. Local contraindication to procedure e.g. local sepsis at the site of intervention, coagulopathy.
6. Patient refusal.

Patients will be randomly assigned and divided into 3 equal comparable groups. Before the procedure, laboratory investigations, Dorsal X-ray, CT and MRI will be done. All Patients will be interviewed and examined by physicians trained in interventional pain management. Patients will be carefully assessed on physical exam for sensory, motor, or reflex deficit and

carefully documented. Patients will be informed about the technique of the blocks, and written informed consents will be obtained.

The types of measures used to assess pain relief will include single rating scales; VAS, and multiple-dimension composite measures; Oswestry Low Back Pain Disability Questionnaire (ODI), The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BM22**.**

**VAS** ; is commonly used to rate various subjective experiences a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end such as "no pain" on the left and "severe pain" on the right, as illustrated in Fig. 1. The patient marks on the line three pain ratings, corresponding to current, best and worst intensity of pain experienced over the past 24 hours.The average of the 3 ratings will be used to represent the patient's level of pain over the previous 24 hours.. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks.

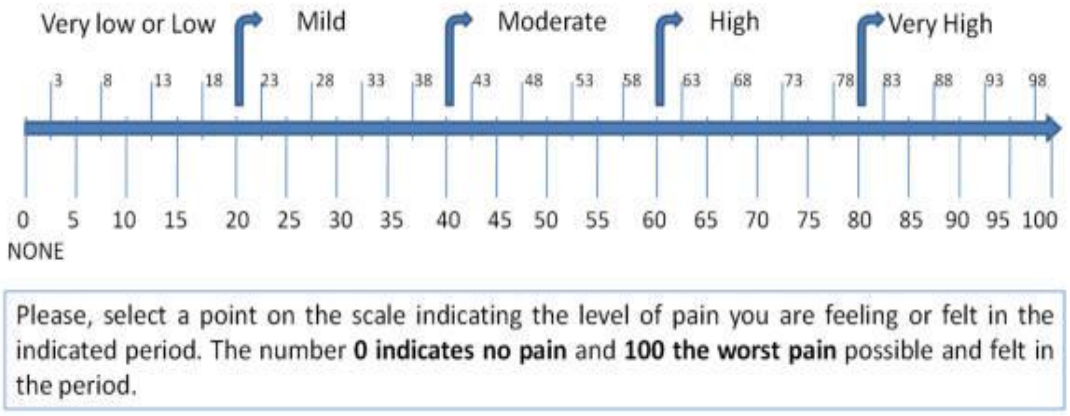


**Fig.(1**) VAS, used in patients diary for guide in self-score pain.

The VAS has consistently demonstrated sensitivity to changes in cancer pain associated with treatment or time ) and usually shows strong associations with other pain intensity ratings, it appears adequately valid and reliable as measures of pain intensity among the many different samples of persons with cancer [17].

**ODI** is a self-administered questionnaire divided into ten sections, each with six items designed to assess limitations of various activities of daily living. Each section is scored on a 0 to 5 scale, with 5 representing the greatest disability. The index is calculated by dividing

the summed score by the total possible score, which is then multiplied by 100 and expressed as a percentage. Thus, for every question not answered, the denominator is reduced by 5. If a patient marked more than one statement for a question, the highest scoring statement is recorded as the true indication of disability. It takes 3.5 to 5 minutes to complete the questionnaire and approximately 1 minute to score. The scores are assessed from 0% to 20% to indicate minimal disability, 20% to 40%, to indicate moderate disability, 40% to 60% to indicate severe disability, 60% to 80% to indicate crippled, and 80% to 100% to indicate bed bound or exaggerating their symptoms [18].The ODI is the most commonly used disease specific patient reported outcome tool to measure functional disability related to back pain [19].

When using only QOL tools as outcome measurement, the majority of cancer studies recommended CP ( Cut point) 1–5 as mild pain, 6 as moderate pain, and 7–10 as severe pain[20]. CPs is defined as the upper bound of a pain intensity category[21] as shown in Fig. (2).



Table 1 CPs for cancer patients

| Author, date and sample size | Pain site and type | Patient type | Pain measured | CPs |
|---|---|---|---|---|
| Serlin *et al.* [1995] (n=1,897) (10) | Metastatic cancer (non-specific origin) | Inpatient and outpatient | Worst pain | 4, 6 |
| Paul *et al.* [2005] (n=160) (19) | Metastatic cancer—bone metastases | Outpatient | Worst pain; average pain | 4, 7; 4, 7 |
| Chow *et al.* [2006] (n=217) (32) | Metastatic cancer—bone metastases | Outpatient | Not specified | 4, 7 |
| Li *et al.* [2007] (n=199) (18) | Metastatic cancer—bone metastases | Outpatient | Worst pain; average pain; current pain | 4, 6; 4, 6; 2, 6 |
| Given *et al.* [2008] (n=588) (33) | Solid tumors or non-Hodgkin's lymphoma | Outpatient | Average pain | 1, 4 |
| Kalyadina *et al.* [2008] (n=148) (25) | Cancer or advanced-stage hematological malignancy | Inpatient and outpatient | Worst pain | 4, 6 |
| Ferreira *et al.* [2011] (n=143) (17) | Cancer with pain | Outpatient | Worst pain | 4, 7 |

CPs, cut points.

**Fig. (2).** Cut points for Cancer Patients.

EORTC has developed one of the most commonly used measurements for this purpose: the **QLQ-C30** which is designed to capture QOL outcomes in a brief internationally recognized and validated tool [22]. EORTC QLQ-C30 (version 3) ,contains 15 relevant items to palliative care from the QLQ-C30, including multi-item physical and emotional function scales, multi-item symptom scales (fatigue and pain), single-item symptom scales (nausea/vomiting, appetite, dyspnea, insomnia, and constipation), and one scale pertaining to perceived overall

QOL. The EORTC **QLQ-BM22** is a sub-module of the QLQ-C30 and is an internationally recognized and validated scale used to measure QOL in bone metastases patients [23]. The QLQ-BM22, includes four subscales: painful sites, pain characteristics, functional interference, and psychosocial aspects. Both questionnaires use a 4-point Likert scale ranging from1 (not at all) to 4 (very much) to rate each item, except for the final 2 question of the QLQ-C30 pertaining to overall QOL which is scored from 1 (very poor) to 7 (excellent). Each subscale is then linearly converted to a score from 0 to 100. For the QLQ-BM22, a higher score indicates worse symptom burden for painful sites and pain characteristics, and better functioning for functional interference and psychosocial aspects. For the QLQ-30, higher scores in the emotional, physical, and QOL scales indicate greater functioning and better [21].

VAS, ODI, QLQ-C30 and QLQ-BM22 will be used to evaluate pain, quality of life, and performance status before the procedure and at 3 days and 1, 3, 6 months after the procedure[24].

In the holding area, midazolam 0.02 mg/kg IV will be given after fixation of a 20 G cannula. All RF procedures will be performed in the hospital outpatient ambulatory care setting using local anesthesia and conscious sedation as necessary, with fluoroscopic guidance to facilitate needle placement. The segmental spinal levels treated will be selected based on the patients' pain referral pattern as determined by history and physical examination findings. After sterile skin preparation, RF will be performed with the patient in the prone position with mild flexion of the spine and the fluoroscopy beam positioned in an antero-posterior (AP) direction. A 10 cm RF needle 20 G with a 10 mm active tip. The image intensifier will be rotated in a cephalo-caudad direction until the endplates of the adjacent thoracic intervertebral discs is lined up and the transverse processes became discernable from the ribs. The needle is then inserted in a slightly medial-cephalad direction under the transverse processes, and using lateral fluoroscopic imaging, incrementally walking into the thoracic intervertebral foramen . The correct position of the needle's tip should be exactly in line with the facet joint spaces on the anteroposterior projection of the image intensifier, and in the posterior part of the foramen on the lateral projection. Once correct needle position is

confirmed by image and since neural tissue cannot be seen on plain radiographs and the DRG may vary with respect to its spatial relationship with the intervertebral foramen, so the location of the needle tip will confirmed not only by image but also by sensory stimulation at 50 Hz. The point of maximum stimulation is where sensory response in the painful dermatome can be elicited with stimuli below 0.5 V intensity and this is designated to be the location of the DRG. Slight redirection can be done to optimize the stimulation; injection of contrast reveals epidural uptake. After establishing the site for the RF, 1 ml 2% lidocaine should be injected through the needle. The needle is then connected to a RF generator (Baylis Medical com. Inc. Canada).

**Group 1**: Patients will receive PRF with temperature 42°C for 480 sec.,2 active cycles per second of 20 milliseconds each , with a voltage output 40 to 60-V range, impedance ranges between 150 and 400 Ohms at all levels using Fluroscopic guidance (FG). The block will be done as that described by **Young-Chang P.** et al [8].

**Group 2**: Patients will receive TRF with temperature 80°C for 90 sec.,2 cycles, using FG . The block will be done as that described by **Ken-ichiro U [16].**

**Group 3**: The control group having identical needle placement and preparation without the RF lesioning (only local anesthetic).

# OUTCOME AND ASSESSMENT

**Primary outcome measure:**

It will include:-

-VAS, ODI, QLQ-C30 and QLQ-BM22 to evaluate pain, quality of life, and performance status at 1, 3, 6 months after the procedure.

**Secondary outcome measures:**

It will include :-

-Neurological defects .

- Dysthesia and hypoesthesia.

- Change in physical activities, and analgesic use.

-Any other complication from either the technique as pneumothorax or local anesthetic, anesthesia dolorosa and burning pain.

-Patients' satisfaction with analgesia through a phone call a week after procedure on 5-level likert scale, (not satisfied at all, only slightly satisfied, somewhat or partly satisfied, very satisfied, perfectly satisfied )

# STATISTICS

## 1 - Sample size estimation:

According to studies [13, 15,16] , to see a significant reduction in VAS defined as at least 50% reduction, ODI, QLQ-C30 and QLQ-BM22 score ($P < 0.01$) with a background standard deviation of 1.0, significance level of 0.05 and power of a test of 80%, minimum number of patients needed would be 25 per group. Because difference in VAS , ODI, QLQ-C30 and QLQ-BM22 score will be more evidenced with control group, the number needed would be much smaller , so the total number needed in the present study would be 69 patients that will be randomized into 3 equal groups. For non-parametric correction, we increased the number to 27 patients for each group.

## 2- Statistical analysis plan:

Data will be analyzed using SPSS version 18.0. Numerical data will be presented as mean, standard deviation or median and range as appropriate. Categorical data will be presented as numbers and proportions. Mixed models ANOVA will be used to show effect of time on pain score and also to evaluate group interaction. Non-parametric tests ; Friedman's test will be used if data did not show normal distribution. Significance level will be considered at 0.05.

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