Retrospective Assessment

Interventional Pain Management for Cancer Pain: An Analysis of Outcomes and Predictors of Clinical Response

Uri Hochberg, MD[1-3], Amir Minerbi, MD, PhD[3-5], Louis-Martin Boucher, MD, PhD[3,6], and Jordi Perez, MD, PhD[3,4]

From: [1]Institute of Pain Medicine, Department of Anesthesia and Critical Care Medicine, Tel Aviv Sourasky Medical Center, Tel-Aviv, Israel; [2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [3]Cancer Pain Clinic, Division of Supportive and Palliative Care, McGill University Health Centre, Montreal, QC, Canada; [4]Alan Edwards Pain Management Unit, McGill University Health Centre, Montreal, QC, Canada; [5]Institute for Pain Medicine, Rambam Health Campus, Haifa, Israel; [6]Department of Diagnostic Radiology, McGill University Health Centre, Montreal, QC, Canada

Address Correspondence:
Uri Hochberg, MD
Cancer Pain Clinic
McGill University, Israel
1001 Decarie Blvd
Montreal, Quebec, H4A 3J1, Canada
E-mail:
urihochberg@hotmail.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 10-14-2019
Revised manuscript received: 02-29-2020
Accepted for publication: 03-30-2020

Free full manuscript:
www.painphysicianjournal.com

Background: Interventional procedures are offered routinely to patients seen in McGill University's interdisciplinary cancer pain management program. However, publications on these procedures are scarce, making it difficult to predict which patients may benefit from them.

Objectives: We hypothesized that interventional pain procedures offered to cancer patients could provide relief of pain as well as other symptoms. Furthermore, some variables may predict the efficacy of such procedures.

Study Design: We conducted a retrospective chart review of interventional pain management procedures.

Setting: The procedures reviewed were conducted at the Cancer Pain Program and performed at the interventional suites of the McGill University Health Centre.

Methods: The retrospective chart review included interventional pain management procedures performed between June 2015 and March 2017. Demographic data, details about the underlying cancer and about the procedure and peripTrocedural patients' reported outcomes were recorded for analysis.

Results: Eighty-two of 126 procedures were included for analysis. Most patients presented with metastatic disease (75%). Eighty percent of the patients reported pain relief, with the average pain severity decreasing by more than 2 points on a 0-to-10 Numeric Rating Scale for pain (from 6.5 of 10 to 4.2 of 10). Forty-three percent of patients were considered responders (≥ 50% pain relief). Responders also reported a significant decrease in fatigue, depression, anxiety, drowsiness, and improved well-being. Among responders, average daily opioid use decreased significantly, by 60% on average. None of the analyzed variables correlated with the response; however, psychosocial variables like anxiety and depression showed a nonsignificant trend towards predicting procedure failure.

Limitations: The core limitations of this study are its size and retrospective nature.

Conclusions: In this cohort of cancer pain patients, interventional cancer pain procedures provided effective pain relief and other benefits, including pain relief, reduced burden of symptoms, and reduction of opioid intake, while demonstrating a favorable safety profile. Patients with poorer ratings of depression and fatigue derived less benefit from procedures, suggesting that offering such procedures as part of patients' treatment plan would be sensible, rather than leaving interventions for later stages.

Key words: Cancer pain, pain management, pain intractable, treatment outcomes, palliative care, advanced cancer, cancer, evidence-based madicine

Pain Physician 2020: 23:E451-E459

Cancer pain: One of the most frequent and distressing side effects of cancer and its treatments is pain (1). A meta-analysis revealed that nearly two-thirds of patients with locally advanced or metastatic cancer suffer from moderate to severe pain, whether during treatment or during advanced stages of their disease (2). Many aspects of patients' well-being are affected by pain, and studies suggest that effective pain control increases patients' willingness to cooperate with treatment and can positively affect patients' willingness to live (3). Thus, pain control may be considered as a matter of the highest priority in the care of individuals with cancer (4), and it has been suggested that management guidelines for cancer pain should be reconsidered and amended to provide a comprehensive treatment as soon as the diagnosis is made (5).

Current challenges to the World Health Organization (WHO)-ladder approach to cancer pain: From its description in 1986, the WHO 3-step ladder has gained wide acceptance in one of the most important public health care issues during the last decades. The WHO ladder principles can be summarized as: "by mouth, by the clock, by the ladder, for the individual and attention to detail" (6).

Despite the effectiveness of the WHO-ladder approach in managing cancer pain, some caveats remain, challenging its utilization. First, there is a paucity of controlled clinical trials assessing its effectiveness (7,8). Second, 10% to 30% of patients treated for cancer pain according to the WHO ladder continue to suffer from poorly managed symptoms. And third, there is considerable variability in the amount of time required to achieve effective analgesia. Finally, despite the years that have elapsed since the publication of the WHO analgesic ladder in 1982, the treatment of cancer pain is often suboptimal (5).

Several modifications of the WHO-ladder approach have been suggested to better adapt it (9). One proposes the elimination of the second step (10). Another recommends the implementation of the "analgesic elevator model" (11), in which the intensity of the pain, rather than the failure to provide pain relief with the previous step, guides the choice of analgesics for patients initially presenting with severe cancer pain. A third change recommends the consideration of interventional pain procedures for patients who did not derive satisfactory pain relief following implementation of the third WHO-ladder step, or who suffered limiting side effects (12). The consideration of interventional pain procedures as a "fourth" step of this ladder has been widely discussed in the literature (12). The benefits of invasive procedures in the management of cancer pain include better understanding of pain mechanisms, immediate and medium-term pain relief without systemic medications, and a more favorable profile of medication-induced side effects (13). Works from recent years have presented the effectiveness of such procedures (14-17). Vissers et al (18) provided evidence-based recommendations for a variety of interventional pain procedures in cancer pain management. Table 1 summarizes these recommendations.

Several predictors of cancer pain relief have been recognized in studies, including reduction in depression, higher socioeconomic circumstances, and fewer comorbid conditions. Patients suffering from severe baseline pain and those with recurring or advanced cancer were less likely to benefit from improvement in pain (19). Data regarding predictive factors of benefit from interventional procedures is scant: predictors of success after celiac plexus neurolysis included functional status and lower daily opioid use (20). Amongst advanced cancer patients with myofascial pain syndrome, the efficacy of trigger point injection was negatively associated with the number of trigger points and positively associated with the area of pain (21).

The interventional approach at the McGill University Cancer Pain Clinic - analysis of our practice: The Cancer Pain Clinic is a joint venture between the Supportive and Palliative Care Service and the Alan Edwards Pain Management Unit at McGill University Health Center (MUHC), Montreal, Canada. The combined effort of the

Table 1. *Recommendations modified from Vissers et al.*

Technique	Evidence	Technique	Evidence
Intrathecal medication delivery	2B+	Neurolytic nervus splanchnicus block	2B+
Epidural medication delivery	2C+	Neurolytic plexus hypogastricus block	2C+
Cervical cordotomy	2C+	Vertebroplasty	2B+
Neurolytic plexus celiacus block	2A+	Kyphoplasty	2B+
Intrathecal phenolization of lower sacral roots or cauda equine			0

Legend: 2 = weak recommendation, 0 = No literature available, only case reports; A = high-quality evidence, B = moderate-quality evidence, C = low-quality evidence; + = positive recommendation

2 units fills the gap between conventional pain management regularly given at the oncologist's office and the comprehensive symptom management plan carried out at palliative care departments.

A description of our interdisciplinary approach to cancer pain has been published (22) whereby analysis of treatments and outcomes demonstrated meaningful relief of pain and other cancer-related symptoms as well as improved disability measures.

Here, we hypothesized that interventional pain procedures offered to cancer patients could provide relief of pain as well as other symptoms. Furthermore, we hypothesized that certain variables may predict the efficacy of an invasive cancer pain procedure.

Methods

This is a retrospective chart review of patients receiving interventional cancer pain procedures; the study received the approval of the Research Ethics Board of the McGill University Health Centre Research Institute.

Charts of all patients seen at the cancer pain clinic between June 2015 and March 2017 were reviewed and patients who received an interventional cancer pain procedure were included.

All of the patients were assessed on a monthly basis (4 ± 2 weeks) at our clinic.

All procedures were performed by trained interventional pain physicians with more than 5 years of intensive practice in the field of cancer pain or by pain fellows under their direct supervision.

All procedures were performed with the assistance of image guidance systems, namely ultrasound and/or fluoroscopy. No diagnostic blocks were done except before nonsympathetic neurolysis (such as epidural or intrathecal neurolysis).

Charts with missing clinical data relevant to this research (i.e., procedure details, pre- or postprocedure pain ratings, opioid consumption) were excluded.

Data was collected for 2 time points: Baseline (the day the procedure was indicated, usually one to 2 weeks before the actual surgical date) and post procedure (during the subsequent visit following the procedure, typically 3 to 6 weeks later).

Data collected included patients' demographics, cancer status, and treatment history. Symptom severity was obtained from the Edmonton Symptom Assessment Scale – revised (ESAS-r) questionnaire (23). Each of the first 9 symptoms was rated with a Numeric Rating Scale from 0 to 10 (NRS-11), with 0 being the least and 10 the worst. The sum of the first 9 items was computed as the ESAS total and used as an overall quality-of-life measure. Data about opioid consumption was collected from the medical reports. For analysis purposes, opioid consumption was converted into morphine equivalent daily dose (MEDD) in milligrams using a standard equivalence equation (24,25). Subanalysis of opioid consumption included comparison of doses from long-acting and short-acting formulations.

Data on postprocedure complications was collected from the medical charts.

For comparison purposes and to allow detailed statistical correlation, a threshold of 50% was selected as the minimum to define a procedure as successful. This strict criterion was chosen over a classical 30% relief response to facilitate differentiation from potential placebo responders. Additionally, previous trials included in evidence-based interventional cancer pain analyses have selected this same threshold (20,22).

All data was collected and analyzed using Microsoft Excel (Microsoft Corporation, Redmond, WA), SPSS Version 24 (IBM Corporation, Armonk, NY}, and Matlab (MathWorks, Natick, MA). Data is expressed as average and standard deviation for quantitative variables and as percentage for qualitative variables. Changes in NRS-11 score and morphine-equivalent dose prior to and post treatment were calculated using a paired 2-tailed t test. Multivariate analysis of variance (MANOVA) was used to analyze the independent variables, followed, where applicable, by individual analysis of variance (ANOVA) with Bonferroni's corrections for each of the independent variables.

Results

During the study time interval, 398 new patients were treated at the clinic, of which 126 underwent interventional procedures for pain relief. Of those, 82 charts satisfied the inclusion criteria, representing 65% of patients undergoing invasive procedures (Fig. 1). Most excluded charts corresponded to patients lacking postprocedural assessments at the cancer pain clinic. These typically belonged to one of 2 groups: patients who experienced very good postprocedural response, not necessitating follow-up visits, or patients with severe residual symptoms, requiring admission and/or transfer of care to another department such as supportive and palliative care.

Patients' demographics, diagnoses, and treatments are presented in Table 2.

Of the patients treated in this study, 75% (n = 62) had metastatic disease and 45% (n = 37) were under-

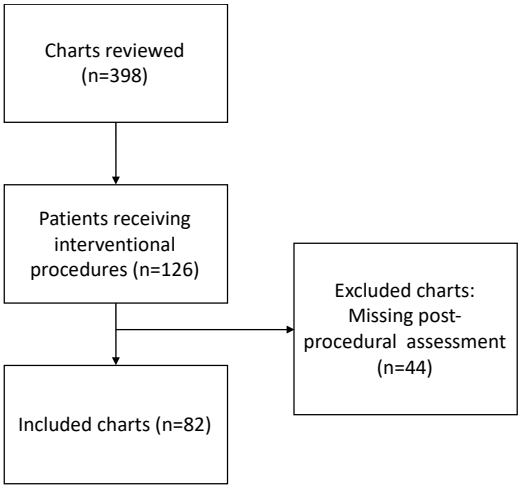

Fig. 1. *A consort diagram of the study.*

Table 2. *Demographic characteristics of study participants, distribution of oncological diagnoses and stage, and type of interventional pain procedure received.*

Age (yrs): Mean ± SD	62.7 (± 11.6)
Gender	46.3% male/ 53.7% female
Cancer site	Gastro-intestinal, n = 31 (37.8%) Lung, n = 12 (14.6%) Breast, n = 10 (12.2%) Urological, n = 10 (12.2%) Hematological, n = 6 (7.3%) Gynecological, n = 5 (6.1%) Musculoskeletal, n = 5 (6.1%) Endocrine, n = 2 (2.4%) Head and Neck, n = 1 (1.2%)
Metastatic disease (yes)	n = 62 (75.6%)
Type of procedure	Spinal blocks, n = 33 (40.2%) Selective nerve root procedures, n = 15 (45.5%) Epidural procedures, n = 10 (30.3%) Lumbar facet procedures, n = 5 (18.2%) Paravertebral procedures, n = 3 (9.1%) Sympathetic blocks, n = 18 (22%) Myofascial/interfascial block, n = 14 (17.1%) Peripheral nerve block, n = 8 (9.8%) Vertebroplasty, n = 4 (4.9%) Sacroiliac joint block, n = 3 (3.7%) Bone cementoplasty/cryolisis, n = 1 (1.2%) Intrathecal catheter placement, n = 1 (1.2%)

Abbreviations: SD, standard deviation

going chemotherapy treatment. Within the 3 months following the procedure, 41% (n = 34) were diagnosed with disease progression and 6% (n = 5) died.

The vast majority of patients (80.5%) reported postprocedural improvement in pain intensity. Average pain scores were significantly reduced from 6.5 ± 2.1 to 4.2 ± 2.7 ($P < .05$) as was self-reported fatigue (5.8 ± 2.2 to 4.9 ± 2.3, $P < .05$).

Other variables included in the ESAS-r questionnaire are shown in Fig. 2A.

Response, defined as postprocedural improvement of 50% or more in reported pain severity, was achieved in 42.6% of patients. Among the frequently performed procedures, sympathetic neurolysis (celiac/splanchnic, hypogastric, and impar ganglion ablation) was associated with the highest response rates (Table 3).

Adverse effects included periprocedural discomfort/pain or short-lasting pain flares. No serious complication was observed. Similarly, none of the patients required a prolonged stay in the recovery area or consultation from the emergency department following a procedure.

Patients responding favorably to an intervention and nonresponders were overall similar in demographics, cancer status, cancer-related treatments, and opioid consumption (Table 4). Significant differences were noted in some symptomatic scores, including fatigue, depression, drowsiness, and ESAS score; however these differences did not retain their significance when corrected for multiple comparisons (Pillai's Trace: F = 1.45; $P = .125$; partial eta squared = 0.44 and Bonferroni correction, see Tables 5 and 6). It is interesting to note that the variables found most predictive of block outcome were related to baseline psychosocial factors (i.e., depression, overall ESAS score).

Discussion

In recent years there has been a growing appreciation of the role of interventional measures in the control of oncologic pain. WHO guidelines recommend the coadministration of non-opioids and other adjuvant drugs in addition to the different steps of the pain ladder. These coanalgesics can be perceived as a metaphoric "handrail" assisting pain care while climbing the pain ladder. Our clinical experience at the MUHC cancer pain clinic suggests that a similar concept could be valuable for the consideration of interventional pain approaches alongside the care of the cancer patient.

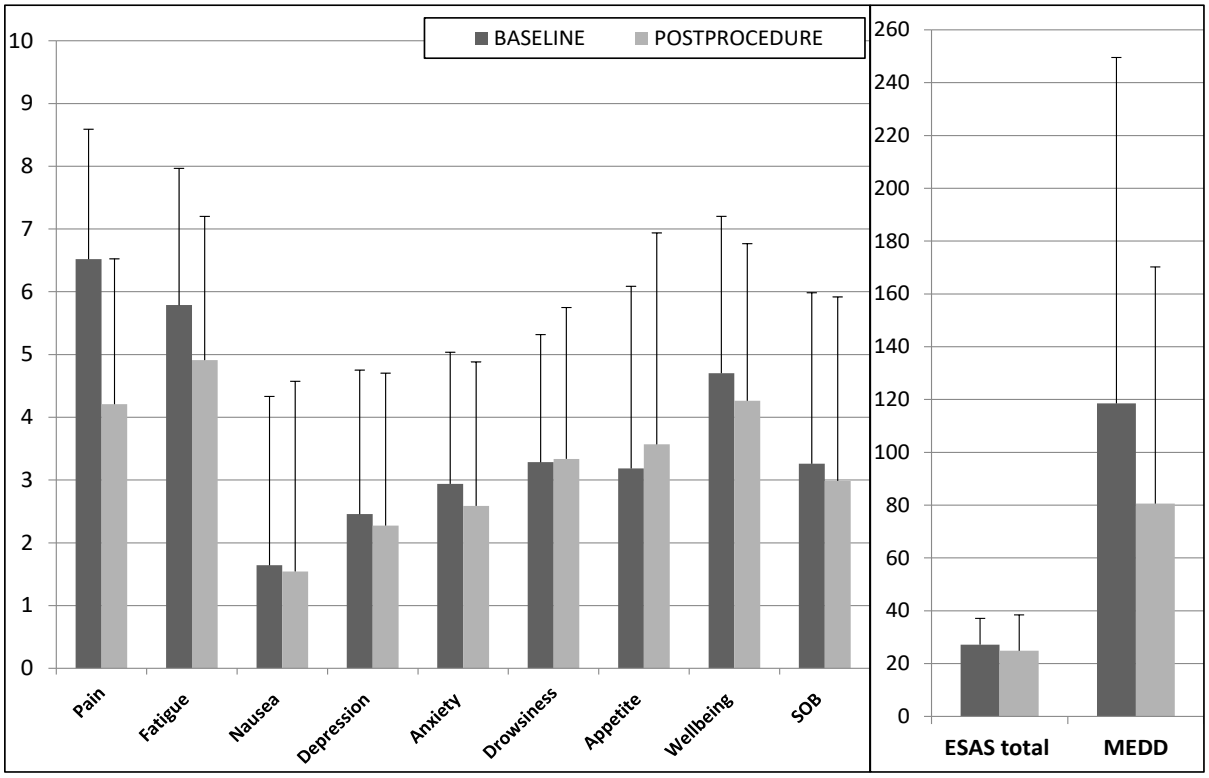

Fig. 2. *Pre- and postprocedural symptoms severity scores in the 9 domains of the ESAS-r questionnaire (A); and average total ESAS-r score and average daily opioid consumption in morphine equivalent daily doses (MEDD, mg) (B).*
Abbreviations: ESAS, Edmonton Symptom Assessment System; MEDD, morphine equivalent daily dose; SOB, shortness of breath.
* Student t test *P* value < .05.

Table 3. *Fraction of patients responding by procedure type.*

Type of Procedure	% Responders
Spinal procedures (n = 33)	36.4%
Sympathetic blocks (n = 18)	61.1%
Myofascial/interfascial block (n = 14)	42.9%
Peripheral nerve block (n = 8)	50%
Vertebroplasty (n = 4)	0%
Sacroiliac joint block (n = 3)	33.3%
Bone cementoplasty/cryolisis (n = 1)	100%
Intrathecal catheter placement (n = 1)	100%

Table 4. *Comparison of baseline variables among responders and nonresponders to interventional pain procedures.*

Baseline Variables	Responders (n = 35)	Nonresponders (n = 47)	Comparison Student t /χ^2
Age (yrs): Mean ± SD	61.9 ± 13.3	62.9 ± 9.2	0.72
Gender (female)	51.1%	57.1%	0.99
Metastatic disease (yes)	71.4%	78.7%	0.99
Baseline pain NRS-11: Mean ± SD	6.6 ± 2.2	6.5 ± 1.9	0.78
Baseline ESAS total Mean ± SD	24.2 ± 9.1	29.3 ± 14.6	0.056
Opioid consumption (MEDD) Mean ± SD	127 ± 87	114 ± 151	0.65

Abbreviations: ESAS, Edmonton Symptom Assessment System; MEDD, morphine equivalent daily dose; NRS-11, Numeric Rating Scale; SD, standard deviation

Our interdisciplinary approach to assessing and managing cancer pain has been previously reported (22). This approach combines pharmacological and nonpharmacological analgesic therapies along with patient-centered care to provide personalized treatment for each case, and is associated with an overall positive response rate (> 50%) in one-third of the patients, with no obvious opioid-sparing effect. In this report, we provide the results of our clinic focusing

Table 5. *Comparison of postprocedural symptoms among responders and nonresponders to interventional pain procedures.*

Postprocedural Symptoms	Responders (n = 35)	Nonresponders (n = 47)	Comparison Student t
Fatigue	3.9 ± 2.5	5.6 ± 2.4	0.002
Nausea	1.1 ± 1.8	1.8 ± 2.9	0.21
Depression	1.2 ± 1.5	3.0 ± 2.94	0.0007
Anxiety	1.7 ± 2.1	3.2 ± 2.8	0.009
Drowsiness	2.5 ± 2.5	3.9 ± 2.5	0.017
Appetite	3.4 ± 3.2	3.6 ± 3	0.76
Well-being	3.0 ± 2.31	5.2 ± 2.3	0.00006
Shortness of breath	2.5 ± 2.5	3.3 ± 2.9	0.25
ESAS total (Mean + SD)	19.3 ± 11.4	28.7 ± 14.8	0.0019

Abbreviations: ESAS, Edmonton Symptom Assessment System

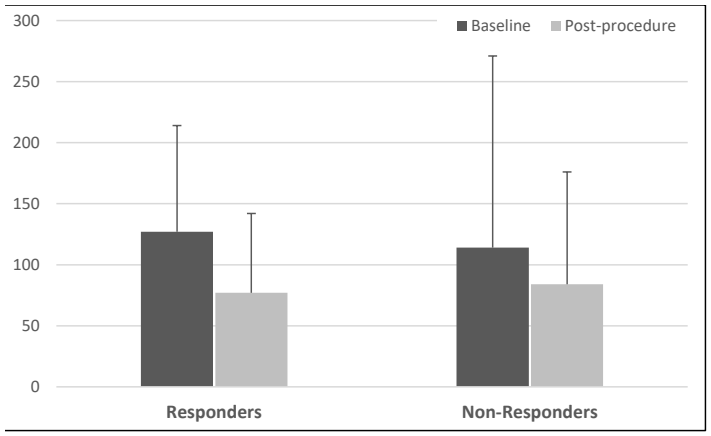

Fig. 3. *Pre- and postprocedural average daily opioid consumption in morphine equivalent daily doses (MEDD, mg) among responders vs nonresponders.*
* Student t test *P* value < .05.

on the interventional arm. Following blocks, average pain scores as well as self-reported fatigue significantly decreased. Response rate among patients receiving pain procedures, defined as ≥ 50% decrease in pain scores, was 42.6%. Furthermore, a second, desired, and important "opioid sparing effect" was observed among responders, as their daily opioid use significantly decreased by an average of 60% (Fig. 3).

Beyond pain relief, responders also reported a significant decrease in fatigue, depression, anxiety, and drowsiness, as well as improved sensation of well-being. In this light it is valuable to mention the lasting psychosocioeconomic burden associated with chronic pain (26), which contributes to the "total pain" experience. Furthermore, pain relief is considered a requirement for a good quality of life (4).

In this study, higher fatigue and depression scores and lower quality of life correlated negatively with response to interventional pain procedures. Additional studies with larger sample sizes are required to validate these observations, and to extensively characterize additional predictors of response to interventional procedures.

The favorable response rate and safety profile of neurolytic and epidural blocks observed here are in line with previous publications and recommendations (18), while the outcome of regional anesthesia procedures (interfascial and peripheral nerve blocks) reported here is in line with a systematic review by the European Association for Palliative Care, highlighting the benefits of regional anesthesia in the management of cancer-related pain (27). The combination of reduced pain, reduced opioid consumption, and improved quality of life have also been observed in recent controlled trials exploring the efficacy of integrating invasive pain procedures in patients with visceral abdominal pain secondary to several types of cancer (28-30).

One could wonder whether the favorable outcome of invasive procedures reported here may be explained by selection bias of patients who are more likely to respond to invasive procedures. Nevertheless, our clinic serves as a referral service for the whole province of Quebec and treats only patients who suffer from intractable pain. Furthermore, treatment outcome was not predictable based on patient- or disease-related variables (Table 3).

Results of this study should be evaluated considering several limitations: first, this is a retrospective chart review study. Furthermore, the study is uncontrolled, owing in part to the fact that most cancer pain patients seen at the MUHC are treated within the MUHC Cancer Pain Centre, making recruitment of patients

treated with a different approach challenging. An additional limitation is the considerable exclusion rate. Most of the cases excluded from this analysis corresponded to patients lacking a postprocedure assessment at the cancer pain clinic. This lack of follow-up could be explained by extreme cases: either patients experiencing very good response to procedures and not needing further assessment, or those not responding to the procedure and presenting with severe symptoms requiring admission or transfer of care to another service like supportive and palliative care. We did not record the cases that required admission following the procedure, which is an additional weakness of this research.

Only the short-term effect of the interventions was recorded, as life expectancy in this group of patients is typically limited, making even temporary pain relief valuable. Further studies should explore the duration of the beneficial effects achieved by those procedures, focusing not only on pain score but on patients' quality of life, functional status, and global impression of change.

Invasive procedures in the management of cancer pain remain (too often, in our view) a last resort. Perceived as a "fourth step" in the ladder, interventional procedures are sometimes considered only for symptoms resistant to any other pharmacological measures. However, as these procedures may allow for a decrease in the consumption of systemic analgesics, thus reducing drug-induced toxicity, a reevaluation of their timing is merited.

All procedures were carried out by the "common practice" approach, as previously published (31). It is possible that the introduction of certain interventional pain procedures in the early stages of comprehensive care of a cancer patient may provide better symptomatic relief. A similar concept advocating early palliative care for patients with metastatic non-small cell lung cancer has been suggested (32). The authors found that early palliative care lead to significant improvements in both quality of life and mood. This was associated with less aggressive care at the end of life and even with longer survival. Restricting these measures to a later stage when curative efforts are exhausted, and patients are often too weak or symptomatic because of disease progression and the side effects of medications, can limit their effectiveness.

Table 6. *Multivariate comparison of baseline variable among responders vs nonresponders to interventional pain procedures.*

Multivariate Analysis	Dependent Variable	*P* Value	Corrected *P* Value (Bonferroni)	Partial Eta Squared
Demographics	Age	.587	1	0.004
	Gender	.858	1	0
Cancer status & treatment	Tumor site	.145	1	0.028
	Metastases	.15	1	0.027
	Intervention	.939	1	0
Symptoms	Pain	.359	1	0.011
	Fatigue	.025	.725	0.064
	Nausea	.241	1	0.018
	Depression	.034	.986	0.058
	Anxiety	.151	1	0.027
	Drowsiness	.017	.493	0.072
	Appetite	.284	1	0.015
	Wellbeing	.078	1	0.04
	Short of breath	.332	1	0.012
	ESAS total score	.029	.841	0.061
Treatments	Chemotherapy	.272	1	0.016
	Surgery	.619	1	0.003
	New diagnosis	.768	1	0.001
	Radiotherapy	.294	1	0.015
	Hospice	.263	1	0.016
	Anticoagulation	.78	1	0.001
Opioids	Morphine	.61	1	0.003
	Oxycodone	.972	1	0
	Hydromorphone	.973	1	0
	Fentanyl	.619	1	0.003
	Methadone	.619	1	0.003
	MEDD	.574	1	0.004
	LA opioids	.205	1	0.021
	SA opioids	.268	1	0.016

Abbreviations: ESAS, Edmonton Symptom Assessment System; LA, long acting; MEDD, morphine equivalent daily dose; SA, short acting

Conclusion

In conclusion, in this cohort of cancer pain patients, interventional procedures in cancer pain management showed positive outcomes, including pain relief, reduced burden of symptoms, and reduction of opioid intake; along with the favorable safety profile of these procedures, this approach seems to represent a net positive balance. We suggest that the indication of interventional procedures along the care process of a cancer patient should be considered as an integrative approach, alongside other measures, rather than an alternative following the failure of other analgesic therapies.

Acknowledgments

Authors want to thank the Louise and Alan Edwards Foundation for their generous support.

References

1. Hochberg U, Perez J, Borod M. New frontier: Cancer pain management clinical fellowship. *Support Care Cancer* 2018; 26:2453-2457.
2. van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. *Ann Oncol* 2007; 18:1437-1449.
3. Von Roenn JH, Cleeland CS, Gonin R, Hatfield AK, Pandya KJ. Physician attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. *Ann Intern Med* 1993; 119:121-126.
4. Strang P. Existential consequences of unrelieved cancer pain. *Palliat Med* 1997; 11:299-305.
5. Breivik H, Cherny N, Collett B, et al. Cancer-related pain: A pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol* 2009; 20:1420-1433.
6. World Health Organization. *Cancer pain relief: With a guide to opioid availability*, 2nd ed. Geneva, Switzerland: World Health Organization; 1996.
7. Jadad AR, Browman GP. The WHO analgesic ladder for cancer pain management. Stepping up the quality of its evaluation. *JAMA* 1995; 274:1870-1873.
8. Ferreira KASL, Kimura M, Jacobsen Teixeira M. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? *Support Cancer Care* 2006; 14:1086-1093.
9. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can Fam Physician* 2010; 56:514-517.
10. Eisenberg E, Shifrin A. Reassessing the need for Step 2 of the WHO Analgesic Ladder. *J Pain Palliat Care Pharmacother* 2011; 25:288-290.
11. Torres LM, Calderón E, Pernia A, Martínez-Vázquez J, Micó JA. From the stairs to the escalator. *Rev Soc Esp Dolor* 2002; 9:289-290.
12. Miguel R. Interventional treatment of cancer pain: The fourth step in the World Health Organization analgesic ladder? *Cancer Control* 2000; 7:149-156.
13. Bhatnagar S. Interventional pain management: Need of the hour for cancer pain patients. *Indian J Palliat Care* 2009; 15:93-94.
14. Mercadante S, Klepstad P, Kurita GP, Sjøgren P, Giarratano A; European Palliative Care Research Collaborative (EPCRC). Sympathetic blocks for visceral cancer pain management: A systematic review and EAPC recommendations. *Crit Rev Oncol Hematol* 2015; 96:577-583.
15. Berger A, Hochberg U, Zegerman A, Tellem R, Strauss I. Neurosurgical ablative procedures for intractable cancer pain. *J Neurosurg* 2019; 10:1-8.
16. Vayne-Bossert P, Afsharimani B, Good P, Gray P, Hardy J. Interventional options for the management of refractory cancer pain—what is the evidence? *Support Care Cancer* 2016; 24:1429-1438.
17. Kurita GP, Sjøgren P, Klepstad P, Mercadante S. Interventional techniques to management of cancer-related pain: Clinical and critical aspects. *Cancers (Basel)* 2019; 11:443.
18. Vissers KPC, Besse K, Wagemans M. Pain in patients with cancer. *Pain Pract* 2011; 11:453-475.
19. Wang HL, Kroenke K, Wu J, Tu W, Theobald D, Rawl SM. Predictors of cancer-related pain improvement over time. *Psychosom Med* 2012; 74:642-647.
20. Yoon DM, Yoon KB, Baek IC, Ko SH, Kim SH. Predictors of analgesic efficacy of neurolytic celiac plexus block in patients with unresectable pancreatic cancer: The importance of timing. *Support Care Cancer* 2018; 26:2023-2030.
21. Hasuo H, Kanbara K, Abe T, Sakuma H, Fukunaga M. Factors associated with the efficacy of trigger point injection in advanced cancer patients. *J Palliat Med* 2017; 20:1085-1090.
22. Perez J, Olivier S, Rampakakis E, Borod M, Shir Y. The McGill University Health Centre Cancer Pain Clinic: A retrospective analysis of an interdisciplinary approach to cancer pain management. *Pain Res Manag* 2016; 2016:2157950.
23. Watanabe SM, Nekolaichuk C, Beaumont C, Johnson L, Myers J, Strasser F. A multicenter study comparing two numerical versions of the Edmonton Symptom Assessment System in palliative care patients. *J Pain Symptom Manage* 2011; 41:456-468.
24. Mercadante S, Caraceni A. Conversion ratios for opioid switching in the treatment of cancer pain: A systematic review. *Palliat Med* 2011; 25:504-515.
25. Walker PW, Palla S, Pei BL, et al. Switching from methadone to a different opioid: What is the equianalgesic dose ratio? *J Palliat Med* 2008; 11:1103-1108.
26. Sessle B. Unrelieved pain: A crisis. *Pain Res Manag* 2011; 16:416-420.
27. Klepstad P, Kurita GP, Mercadante S, Sjogren P. Evidence of peripheral nerve blocks for cancer-related pain: A systematic review. *Minerva Anestesiol* 2015; 81:789-793.
28. De Oliveira R, Dos Reis MP, Prado WA. The effects of early or late neurolytic sympathetic plexus block on the management of abdominal or pelvic cancer pain. *Pain* 2004; 110:400-408.

29. Wise JM, Carone M, Paquin SC. Randomized, double-blind, controlled trial of early endoscopic ultrasound–guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. *J Clin Oncol* 2011; 29:3541-3546.

30. Okuyama M, Shibata T, Morita T. A comparison of intraoperative celiac plexus block with pharmacological therapy as a treatment for pain of unresectable pancreatic cancer. *J Hepatobiliary Pancreat Surg* 2002; 9:372-375.

31. Rathmell JP. *Atlas of image-guided intervention in regional anesthesia and pain medicine.* Lippincott Williams & Wilkins, Philadelphia, PA, 2011.

32. Temel JS, Greer JA, Muzikhansky A, et al. Early palliative care for patients with metastatic non–small-cell lung cancer. *N Engl J Med* 2010; 363:733-742.