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ORIGINAL RESEARCH

A Delphi Study on the Management of Neuropathic Cancer Pain in Spain: The DOLNEO Study

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Purpose: The objectives of this project were to assess the current situation and management of cancer-related neuropathic pain (CRNP) in Spain and to provide specific recommendations for the assessment, diagnosis and treatment of CRNP using a Delphi methodology.

Methods: This was a qualitative study that followed a Delphi methodology using a questionnaire with 56 statements that were grouped into 5 areas related to CRNP: prevalence and impact, pathophysiology, assessment and diagnosis, specific syndromes, treatment, and multidisciplinary approach. Based on the responses, the scientific committee prepared an algorithm and a recommended pathway for the management of CRNP.

Results: Seventy-nine physicians attended the meeting and completed the questionnaire. Consensus was reached for all statements relating to the prevalence and impact of CRNP. However, the perceptions of specialists from palliative care of the frequency and impact of CRNP differed from those of other specialists. A high degree of consensus was reached for all statements concerning the assessment and diagnosis of CRNP. Regarding specific syndromes, the only statement with a lack of consensus was that on the frequency of NP in patients undergoing radiotherapy. There were some disagreements regarding the multidisciplinary approach and referral criteria for the management of NP.

Conclusion: Our results show a large degree of agreement on the assessment, diagnosis and treatment of cancer-related neuropathic pain among the specialists involved in its management. There were, however, some disagreements regarding the multidisciplinary approach and referral criteria for the management of neuropathic pain.

Keywords: cancer-related neuropathic pain, prevalence, diagnosis, treatment, consensus

Plain Language Summary

The objectives of this project were to assess the current situation and how cancer-related neuropathic pain is diagnosed and treated in Spain and to provide specific recommendations for the assessment, diagnosis and treatment. For doing so, we asked the opinion on fifty-six specific issues to a group of seventy-nine physicians who deal with cancer-related neuropathic pain. Our results show a large degree of agreement on the assessment, diagnosis and treatment of cancer-related neuropathic pain among the specialists involved in its management. There were, however, some disagreements regarding the multidisciplinary approach and referral criteria for the management of neuropathic pain.

Introduction

Neuropathic pain, defined as "pain caused by a lesion or disease of the somatosensory nervous system",[1] is common in patients with cancer and has an important impact on the patient's functioning. A systematic review that included 14

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studies with a confirmatory evaluation of the sensory abnormality or diagnostic lesion—a requirement for the diagnosis of neuropathic pain—reported a prevalence of neuropathic pain among patients with cancer ranging from 19% as a conservative estimate to 39% when patients with mixed pain were considered.[2] More recently, a systematic review of 29 studies reporting data on cancer-related neuropathic pain (CRNP) estimated a pooled prevalence of 31%.[3] In patients with cancer pain, the presence of a neuropathic component is associated with a higher incidence of breakthrough pain, longer pain duration, higher pain intensity and greater interference with patients' daily activities.[4–6] Even after controlling for disease stage, cancer duration, radiotherapy, chemotherapy and comorbidities, the presence of CRNP is associated with a deterioration in quality of life.[7] Compared to patients with pain of nociceptive origin, patients with CRNP exhibit greater analgesic requirements, worse performance status, and poorer physical, cognitive and social functioning.[8]

The etiology of CRNP is very heterogeneous and can broadly be categorized as disease-related (eg, tumor-related bone pain) or treatment-related neuropathic pain that can be secondary to surgery, radiotherapy or chemotherapy interventions.[9,10] The adequate diagnosis of CRNP is key for establishing an optimal treatment strategy.[11] However, the diagnosis of neuropathic pain in patients with cancer is complicated by the presence of coexisting processes, such as neurological disease or muscle spasticity, that may confuse the clinical picture, leading to underrecognition and, consequently, undertreatment of this clinical condition.[10] This is further complicated in the case of chemotherapy-induced neuropathic pain (CINP) due to underreporting; therefore, adequate anamnesis is essential for identifying the origin of CRNP. Several studies have reported that patients with CRNP are not adequately treated, with a high proportion of patients not receiving adjuvant analgesics, less than half of patients receiving drugs from steps 2 and 3 of the WHO's cancer pain ladder for adults, and in patients with mixed pain, a lack of treatment of the neuropathic component.[5–7,12]

The lack of specific clinical practice guidelines on the management of CRNP could have contributed to the above-mentioned situation. In 2013–2014, a group of experts published their analysis of 9 European clinical practice guidelines that mentioned the management of CRNP.[13–15] The authors reported great heterogeneity regarding the recommendations on diagnosis and assessment.[14] Regarding treatment, the majority of guidelines based their recommendations on the extrapolation of data from noncancer publications without considering the specific situation of cancer patients,[15] with the exception of some specific guidelines for CINP.[16,17] Although the picture has improved and more recent guidelines on cancer pain devote a specific section to CRNP,[18,19] only the European Society of Medical Oncology includes a treatment algorithm.[18] Additionally, there is still a need for a comprehensive guide fully devoted to the management of CRNP. The American Society of Clinical Oncology also issued a guideline in 2020, but it is focused on CINP.[20]

The objectives of this project were to assess the current situation and management of CRNP in Spain and to provide specific recommendations for the assessment, diagnosis and treatment of CRNP using a Delphi methodology.

Materials and Methods

The DOLNEO ("DOLor NEuropatico Oncológico"; neuropathic pain in oncology) study was a qualitative study that followed a Delphi methodology, as explained below. The study was revised and approved by the Ethics Committee of the University Hospital "La Princesa" (Reference number 3789, 23-05-19, acta CEIm 10/19; Madrid, Spain).

Selection of Experts and Development of the Questionnaire

The scientific committee comprised two experts: a pain physician from a pain unit and a medical oncologist with broad experience in the management of cancer pain, including CRNP. Seventy-nine physicians from several specialties were selected by the scientific committee from the main hospitals throughout Spain, including physicians from pain units, medical oncology, radiation therapy and palliative care departments/units. They were invited to participate in the project via e-mail. They did not receive any incentive for their participation.

A literature search on CRNP was performed and revised by the scientific committee. Based on that revision and the key elements mentioned in a recent Spanish guideline for the interdisciplinary approach to cancer pain,[21] they prepared a questionnaire containing 56 statements that were grouped into 5 areas: prevalence and impact, pathophysiology, assessment and diagnosis, specific syndromes, treatment and multidisciplinary approach to CRNP. The specific

references from which the statements were extracted are shown in the results section. The questionnaire included a section requesting information on participant characteristics and background, including information on age, sex, geographic area, type of center (ie, public, private, mixed), years of experience, current medial specialty, whether they have had experience as a trainer on CRNP in the current year (2019), whether they have participated in any research on CRNP in the current year (2019) and the number of patients with CRNP they have seen in the last month. The second section of the questionnaire contained the 56 statements that had to be answered on a 5-point Likert scale: 1=fully disagree, 2=disagree, 3=neither agree nor disagree, 4=agree, 5=fully agree.

The Delphi Consensus Process

The Delphi method is a frequently used system to gather opinions in a structured way from a group of experts.[22] The key characteristics of the method are the anonymous nature of the survey and that the participants receive feedback on their answers and may adjust their initial answers to that feedback using an iterative process.[22]

Two rounds of the survey were performed. For the first round, all participants attended a one-day meeting in Madrid (Spain). During the meeting, the scientific committee facilitated a discussion with all the attendees on the topics of the project that comprised all the items included in the questionnaire. After finalizing the meeting, the participants had to answer the questionnaire anonymously through a website specifically designed for the project. In the second round, the participants received via e-mail the results of the statistical analysis of the first round and a request to complete a second questionnaire that comprised only those questions where consensus (see definition below) was not reached in the first round.

The Algorithm and Pathway for the Management of CRNP

The final results of the consensus were reviewed by the scientific committee, who, based on the responses, prepared an algorithm for the management of CRNP and a recommended pathway for the management of these patients.

Statistical Analysis

Analysis of the questionnaire was performed using descriptive statistics. Thus, the absolute and relative frequencies for each answer were calculated. We considered that consensus was reached when at least 75% of the answers indicated that they fully agreed or agreed or fully disagreed or disagreed; this cut-off point for consensus has been used by other authors such as the American Society of Clinical Oncology.[23] In addition, the median was also calculated to indicate the strength of the consensus. To compare some responses across the specialties involved in the study, the Kruskal–Wallis test was applied.

All analyses were performed using SAS, version 9.1.3 Service Pack 3.

Results

Participants

Seventy-nine physicians attended the meeting and completed the questionnaire. Although participants were working in 16 of the 17 geographic regions, one-fourth of them were working in Madrid. Participants were evenly distributed regarding sex and had a mean (SD) age of 44.7 (11.6) years. Most of them were working in a public (n=59, 74.7%) or mixed (n=13, 16.5%) center. The specialties involved among the 75 participants who answered that question were anesthesiologists/pain physician (38.7%), radiation oncology (25.3%), medical oncology (21.3%), palliative care (13.3%) and neurology (1.4%). The mean (SD) years of experience was 14.6 (10.3). In the current year (2019), 23 (29.1%) of the respondents had participated as a lecturer in training on CRNP, and 17 (21.5%) had participated in other research on CRNP. Regarding the number of patients with CRNP treated in the last month, 36 (45.6%) treated 0–10 patients, 26 (32.9%) treated 11–20 patients, 8 (10.1%) treated 20–30 patients and 4 (5.06%) treated more than 30 patients (in 5 [6.3%], this result was missing). The number of patients with CRNP treated in the last month was higher among respondents of the palliative care and pain units (data not shown).

Prevalence and Impact of CRNP

There was consensus on all the statements of this section. The strength of the consensus was somewhat weaker (ie, a median of 4 instead of a median of 5) for most of the questions related to prevalence (Table 1).

Regarding the statement on the frequency of moderate to severe pain, respondents from palliative care units showed a greater degree of agreement, with a median of 5 on that statement compared to a median of 4 for the respondents of

Table 1 Results of the Delphi Consensus Process for the Statements on the Prevalence and Impact of Cancer-Related Neuropathic Pain

Statement	N	Degree of Agreement					
		1	2	3	4	5	Median
1. Pain is prevalent in cancer patients: 64% in patients with metastasis or an advanced stage of the disease, 59% in patients on anticancer treatment and 33% in patients after curative treatment.[32]	69	9 (13.0%)	0 (0.0%)	1 (1.4%)	31 (44.9%)	28 (40.6%)	4
2. One-third of cancer patients rated their pain as moderate to severe.[32]	73	0 (0.0%)	4 (5.5%)	1 (1.4%)	45 (61.6%)	23 (31.5%)	4
3. 20% of cancer pain is purely neuropathic. However, if mixed nociceptive-neuropathic pain is included, approximately 40% of cancer patients are affected by neuropathic pain.[10,33]	74	1 (1.4%)	4 (5.4%)	3 (4.1%)	37 (50.0%)	29 (39.2%)	4
4. Neuropathic cancer pain (CRNP) can be classified according to its etiology, based on disease, disease-related, related with cancer treatment and/or regardless of cancer (comorbidities), according to its location, according to the timing and according to its temporality.[34]	76	0 (0.0%)	0 (0.0%)	1 (1.3%)	35 (46.1%)	40 (52.6%)	5
5. The onset of chemotherapy-induced neuropathic pain (CINP) is a limiting factor in the treatment of cancer. It can cause delays in the administration of a new cycle, reduction of cycle doses or even reduced therapy.[35]	79	0 (0.0%)	1 (1.3%)	2 (2.5%)	19 (24.1%)	57 (72.2%)	5
6. CRNP is a common complication of cancer, and it is often undernotified, underdiagnosed and undertreated.[12]	79	0 (0.0%)	0 (0.0%)	1 (1.3%)	19 (24.1%)	59 (74.7%)	5
7. CRNP has an impact on patients' quality of life and worsens mood, affecting their response to treatment (lower response) and influencing the evolution of their disease.[36]	79	0 (0.0%)	1 (1.3%)	4 (5.1%)	28 (35.4%)	46 (58.2%)	5
8. Chemotherapy-induced neuropathic pain (CINP) has a prevalence of 68% in the first month after the end of chemotherapy, 60% at three months and 30% at 6 months or later.[37]	75	0 (0.0%)	5 (6.7%)	9 (12.0%)	40 (53.3%)	21 (28.0%)	4
9. The prevalence of CRNP varies depending on the location of the tumor, and it is more frequent in head and neck tumors (70%), gynecological and gastrointestinal tumors (60%), breast, lung and urogenital tumors (50–55%).[38]	78	0 (0.0%)	0 (0.0%)	4 (5.1%)	29 (37.2%)	45 (57.7%)	5

Notes: Degree of agreement was evaluated using a 5-point Likert scale: 1=fully disagree, 2=disagree, 3=neither agree nor disagree, 4=agree, 5=fully agree.

each of the other specialties; however, the distribution of the responses did not significantly differ across the specialties (data not shown). Respondents from palliative care and pain units (100%) agreed that CRNP has an impact on patients' quality of life and worsens mood, decreasing their response to treatment and influencing the evolution of their disease, and the degree of agreement was lower in other specialties (p=0.0002).

Pathophysiology of CRNP

Consensus was reached on all 4 statements of this section, with a median of 5 on all statements, with the exception of the mitochondrial toxicity hypothesis as the main cause of chemotherapy-induced neuropathic pain (Table 2).

Assessment and Diagnosis of CRNP

There was consensus on all 8 statements, with a median of 5, except on the general statement on the difficulties associated with CRNP diagnosis due to the lack of standardized diagnostic tools; eleven (14.0%) disagreed with the presence of those difficulties (Table 3).

Specific Syndromes of CRNP

In all but one of the statements regarding the specific syndromes, there was consensus (Table 4). The statement without consensus concerns the prevalence of radiotherapy-induced neuropathic pain, which stated that "of breast cancer patients undergoing radiotherapy treatment, 21–65% will develop chronic neuropathic pain". Eighteen (25%) of the respondents disagreed with the statement. When analyzing this statement by specialty, the distribution of the responses was almost identical across all specialties, with a proportion of respondents who disagreed ranging from 19.2% among physicians from pain units to 27.8% among those from radiation oncology.

Treatment for Patients with CRNP

The respondents agreed with all 8 statements regarding the treatment of CRNP, with a high degree of consensus on most of the statements (Table 5).

Table 2 Results of the Delphi Consensus Process for Statements on the Pathophysiology of Cancer-Related Neuropathic Pain

Statement	N	Degree of Agreement					
		1	2	3	4	5	Median
10. The pathophysiology of the NP is complex and largely unknown.[39,40]	75	0 (0,0%)	1 (1,3%)	1 (1,3%)	28 (37,3%)	45 (60,0%)	5
11. CRNP most commonly coexists with other painful conditions with inflammatory, visceral, ischemic and/or nociceptive pathophysiology.[39,40]	75	0 (0,0%)	0 (0,0%)	3 (4,0%)	33 (44,0%)	39 (52,0%)	5
12. In pure CRNP, we can differentiate a first moment of peripheral sensitization (reversible) that if perpetuated leads to a central sensitization (hardly reversible).[39,40]	76	0 (0,0%)	0 (0,0%)	4 (5,3%)	22 (28,9%)	50 (65,8%)	5
13. Studies on CINP in experimental animal models have resulted in the mitochondrial toxicity hypothesis, which postulates that the main cause for this type of chronic peripheral neuropathy is a toxic effect on the mitochondria in primary afferent somatosensory neurons.[41]	76	0 (0,0%)	0 (0,0%)	12 (15,8%)	29 (38,2%)	35 (46,1%)	4

Notes: Degree of agreement was evaluated using a 5-point Likert scale: 1=fully disagree, 2=disagree, 3=neither agree nor disagree, 4=agree, 5=fully agree.

Table 3 Results of the Delphi Consensus Process for the Statements on the Assessment and Diagnosis of Cancer-Related Neuropathic Pain

Statement	N	Degree of Agreement					
		1	2	3	4	5	Median
14. Determining the presence of NP is not easy since there are no standardized diagnostic tools for NP diagnosis.[11]	79	4 (5,1%)	7 (8,9%)	5 (6,3%)	26 (32,9%)	37 (46,8%)	4
15. Early prevention and recognition of CRNP are crucial to avoid serious and disabling types.[37]	78	0 (0,0%)	0 (0,0%)	3 (3,8%)	15 (19,2%)	60 (76,9%)	5
16. A recent systematic review on the analysis and quality of tools used for NP assessment and quality in cancer patients identifies the concordance between clinical diagnosis and the results of the screening tools LANSS, DN-4 and pain detect.[11]	75	1 (1,3%)	2 (2,7%)	7 (9,3%)	26 (34,7%)	39 (52,0%)	5
17. Diagnosis of NP in cancer patients is essential to prevent or decrease neurotoxic events after cancer treatment, especially when chemotherapy is administered, and to facilitate a pathophysiology-based approach as well as to suggest an optimal pain treatment.[14]	77	0 (0,0%)	1 (1,3%)	4 (5,2%)	21 (27,3%)	51 (66,2%)	5
18. Predictive factors for CRNP are female gender, youth, increased BMI, more advanced cancer stage, perineural invasion, chemotherapy or invasive surgeries, genetic polymorphisms associated with increased sensitivity to pain, depression, anxiety, stress, sleep disorders, low socioeconomic status, multifocal pain and perioperative pain intensity.[28]	77	0 (0,0%)	1 (1,3%)	2 (2,6%)	12 (15,6%)	62 (80,5%)	5
19. Looking for symptoms and signs showing injury in the somatosensory system is essential at diagnosis: - positive symptoms: allodynia, hyperalgesia, dysesthesia, paraesthesia, spontaneous pain and evoked pain. - Negative symptoms: hypoesthesia, analgesia.[21]	77	1 (1,3%)	1 (1,3%)	2 (2,6%)	11 (14,3%)	62 (80,5%)	5
20. Early detection should be based on sensory symptoms, rather than loss of reflexes or motor changes.[12]	72	1 (1,4%)	0 (0,0%)	2 (2,8%)	22 (30,6%)	47 (65,3%)	5
21. The correct assessment of pain is considered one of the key aspects when prescribing a certain treatment with the aim of controlling it as well as improving the patient's quality of life.[21]	76	0 (0,0%)	0 (0,0%)	1 (1,3%)	9 (11,8%)	66 (86,8%)	5

Notes: Degree of agreement was evaluated using a 5-point Likert scale: 1=fully disagree, 2=disagree, 3=neither agree nor disagree, 4=agree, 5=fully agree.

Multidisciplinary Approach and Referral Criteria for the Management of CRNP

There was consensus on all other statements about referral criteria (Table 6), with the exception of the statement that "their hospital facilities do not guarantee a correct approach to their patients with cancer pain", with which 40% of

Table 4 Results of the Delphi Consensus Process for the Statements on Specific Syndromes of Cancer-Related Neuropathic Pain

Statements	N	Degree of Agreement					
		1	2	3	4	5	Median
22. The main risk factor in the development of chemotherapy-induced neuropathy is dose and duration of treatment.[35]	73	0 (0,0%)	0 (0,0%)	1 (1,4%)	14 (19,2%)	58 (79,5%)	5
23. The type of chemotherapy influences the risk of developing chemotherapy-induced neuropathic pain (CINP). Although it is predominantly a sensory neuropathy, autonomous function may be affected; there is evidence of sensory fibres and there is a reduction in the density of epidermal fibres.[42]	76	1 (1,3%)	1 (1,3%)	3 (3,9%)	19 (25,0%)	52 (68,4%)	5
24. In platinum-related CINP, around 28% of patients develop symptomatic neuropathies, of which 6% suffer from disabling polyneuropathies,[43–45]	76	2 (2,6%)	2 (2,6%)	4 (5,3%)	27 (35,5%)	41 (53,9%)	5
25. Peripheral neuropathy may develop and worsen several months after chemotherapy discontinuation in 30% of patients (coasting or dragging)..[43–45]	77	0 (0,0%)	0 (0,0%)	1 (1,3%)	15 (19,5%)	61 (79,2%)	5
26. Oxaliplatin is the most common drug involved in the development of peripheral neuropathy.[43–45]	78	2 (2,6%)	1 (1,3%)	1 (1,3%)	15 (19,2%)	59 (75,6%)	5
27. With the repetition of platinum-based chemotherapy cycles, 50 to 70% of patients develop persistent peripheral neuropathy, which manifests as a symmetrical, distal, mainly sensory polyneuropathy characterized by the persistence of paraesthesia between chemotherapy cycles, numbness in hands and feet and neuropathic pain.[43–45]	78	0 (0,0%)	2 (2,6%)	6 (7,7%)	11 (14,1%)	59 (75,6%)	5
28. In CINP caused by Vinca alkaloids, around 50% of patients experience sensory-motor peripheral neuropathies, including numbness and tingling in hands and feet with paraesthesia and dysesthesia and loss of deep tendon reflexes.[46,47]	79	0 (0,0%)	1 (1,3%)	3 (3,8%)	20 (25,3%)	55 (69,6%)	5
29. Sensory, motor, distal and symmetrical neuropathy caused by Vinca alkaloids occurs at the beginning of treatment, within 2 weeks.	77	0 (0,0%)	2 (2,6%)	13 (16,9%)	28 (36,4%)	34 (44,2%)	4
30. Sensory neuropathy as well as paraesthesia in hands and feet, mainly caused by the use of taxanes (70–95% incidence), occur at the beginning of treatment.[35]	72	0 (0,0%)	7 (9,7%)	3 (4,2%)	29 (40,3%)	33 (45,8%)	4
31. Changes caused by Vinca alkaloids cause sensory neuropathy that is usually reversible, although the recovery period can be long.[48]	75	0 (0,0%)	3 (4,0%)	6 (8,0%)	29 (38,7%)	37 (49,3%)	4
32. Paclitaxel treatment may result in early sensory neuropathy (24–72 hours after the administration of a single high dose) in 59–78% of patients.[44]	78	0 (0,0%)	4 (5,1%)	6 (7,7%)	26 (33,3%)	42 (53,8%)	5

(*Continued*)

Table 4 (Continued).

Statements	N	Degree of Agreement					
		1	2	3	4	5	Median
33. Sensory neuropathy caused by paclitaxel is dose-dependent, and it is also influenced by the duration of the infusion (short duration).[44]	77	0 (0,0%)	1 (1,3%)	3 (3,9%)	28 (36,4%)	45 (58,4%)	5
34. Sensory neuropathy caused by paclitaxel causes paraesthesia, numbness, tingling and burning, with mechanical and cold allodynia.[44]	77	1 (1,3%)	2 (2,6%)	1 (1,3%)	21 (27,3%)	52 (67,5%)	5
35. Up to 80% of patients treated with paclitaxel maintain sensory neuropathy after finishing treatment.[44]	78	0 (0,0%)	2 (2,6%)	9 (11,5%)	25 (32,1%)	42 (53,8%)	5
36. Between 20% and 69% of breast cancer survivors develop chronic NP, often from surgery-related damage to the axillary or intercostobrachial nerves.[21]	78	0 (0,0%)	3 (3,8%)	3 (3,8%)	28 (35,9%)	44 (56,4%)	5
37. The incidence of chronic pain 3 and 6 months after a thoracotomy is 57% and 47%, respectively.[21]	78	0 (0,0%)	3 (3,8%)	7 (9,0%)	30 (38,5%)	38 (48,7%)	4
38. Of breast cancer patients undergoing RT treatment, 21–65% will develop chronic NP.[28]	72	5 (6,9%)	13 (18,1%)	7 (9,7%)	30*(41,7%)	17* (23,6%)	4*
39. Following Cx and RT treatments of head and neck cancers, mixed syndromes are common.[28]	78	0 (0,0%)	1 (1,3%)	0 (0,0%)	24 (30,8%)	53 (67,9%)	5
40. Pain is usually the primary symptom of neoplastic involvement of the brachial plexus and usually begins as a deep shoulder pain that radiates to the medial arm and hand.[49,50]	78	1 (1,3%)	1 (1,3%)	3 (3,8%)	24 (30,8%)	49 (62,8%)	5
41. In brachial plexus neoplasm, neurological symptoms and signs reflect the involvement of nerve roots C8 and T1 with paraesthesia and sensory loss in the hand and medial area of the arm and intrinsic muscle weakness of the hand.[49,50]	77	2 (2,6%)	1 (1,3%)	1 (1,3%)	22 (28,6%)	51 (66,2%)	5
42. In lumbosacral plexopathy, pain is the primary symptom, usually dull and diffuse, that is located in the lower back or buttock and can radiate down the leg.[21]	77	1 (1,3%)	1 (1,3%)	1 (1,3%)	18 (23,4%)	56 (72,7%)	5

Notes: Degree of agreement was evaluated using a 5-point Likert scale: 1=fully disagree, 2=disagree, 3=neither agree nor disagree, 4=agree, 5=fully agree. *Items with lack of consensus.

respondents disagreed. When analyzed by treatment specialty, medical oncology respondents showed the highest proportion of disagreement (67%), whereas those from radiation oncology showed the lowest percentage (22%), although the differences across specialties were not statistically significant (p=0.1131).

There were some other differences across specialties regarding the multidisciplinary approach to the management of CRNP. There was consensus that the "collaboration between the Pain Unit and the Medical Oncology Unit seems appropriate to address cancer pain" for medical oncology (93%), pain physicians (100%) and palliative care (80%) but not among respondents from radiation oncology (44%) (p<0.0001 for the comparison across specialties). Although the differences were not statistically significant across specialties, the proportion of agreement with the statement "I am prepared to take care of patients with cancer pain" was 75% for pain physicians compared to 94% for medical oncology, 88% for radiation oncology and 100% for palliative care (p=0.1468).

Table 5 Results of the Delphi Consensus Process for the Statements on the Treatment of Cancer-Related Neuropathic Pain

Statements	N	Degree of Agreement					
		1	2	3	4	5	Median
43. Evidence for the management of CRNP is limited.[10]	74	1 (1,4%)	2 (2,7%)	2 (2,7%)	20 (27,0%)	49 (66,2%)	5
44. There is no clear consensus on the 1st line treatment, which is a challenge for clinicians and patients.[10]	76	2 (2,6%)	2 (2,6%)	3 (3,9%)	20 (26,3%)	49 (64,5%)	5
45. Duloxetine is the only treatment with enough evidence to recommend its use in oxaliplatin-related CIPN.[16]	72	0 (0,0%)	2 (2,8%)	11 (15,3%)	35 (48,6%)	24 (33,3%)	4
46. Early diagnosis and treatment of CIPN is the best and only tool available to prevent its progression to disabling neuropathy.[35]	75	1 (1,3%)	1 (1,3%)	4 (5,3%)	15 (20,0%)	54 (72,0%)	5
47. Treatment of patients with CIPN should be based on two pillars: prevention (dose adjustment and neuroprotection) and symptomatic relief.[42]	76	2 (2,6%)	1 (1,3%)	9 (11,8%)	17 (22,4%)	47 (61,8%)	5
48. According to mitochondrial toxicity hypothesis, drugs that protect or restore mitochondrial function could help preventing and treating distal and symmetrical peripheral neuropathies.[41]	74	0 (0,0%)	0 (0,0%)	14 (18,9%)	26 (35,1%)	34 (45,9%)	4
49. Clinically, high-dose 8% capsaicin patches have been used for peripheral neuropathic pain. Although high-grade evidence for its use in CIPN is limited, there are reports of its efficacy.[42]	75	0 (0,0%)	3 (4,0%)	2 (2,7%)	27 (36,0%)	43 (57,3%)	5
50. Topical treatments get better response in positive symptoms and signs compared to systemic drugs (eg, allodynia, dysesthesia, lancinating seizures and urgent pain).[51]	74	0 (0,0%)	0 (0,0%)	4 (5,4%)	28 (37,8%)	42 (56,8%)	5

Notes: Degree of agreement was evaluated using a 5-point Likert scale: 1=fully disagree, 2=disagree, 3=neither agree nor disagree, 4=agree, 5=fully agree.

The Algorithm and Pathway for the Management of CRNP

Based on the results, we propose a treatment algorithm and clinical pathway, which are presented in Figures 1 and 2, respectively. The treatment algorithm reflects that the pharmacological approach to neuropathic pain in cancer patients must be clearly differentiated depending on the etiology of the pain, distinguishing 3 scenarios. The first scenario is pain due to the disease itself, whose approach is mainly based on the treatment of the tumor, associated with opioids in first-line treatment and other drugs or adjuvant treatments such as corticosteroids. The second is neuropathic pain related with cancer treatment; in these cases, the first-line treatment would be duloxetine at a dose of 60 mg and second-line options comprised anticonvulsants (ie pregabalin, gabapentin), other antidepressants (eg venlafaxine, amitriptyline) or topical treatments (Capsaicin 8%, Baclofen + Amitriptyline + Ketamine). The third scenario is neuropathic pain occurring in the context of a patient with cancer, but not related with the disease itself or its treatment (eg postherpetic neuralgia, diabetic neuropathy); the treatment of these latter cases should follow the recommendations included in the clinical practice guidelines for neuropathic pain, with first lines of dual/tricyclic antidepressants and anticonvulsants, second line with topical treatments and third line opioids.

Discussion

Although consensus was reached for all statements relating to the prevalence and impact of CRNP, it was somewhat weaker for statements on prevalence. This probably reflects the different experiences of several specialists with

Table 6 Results of the Delphi Consensus Process for the Statements on the Referral Criteria for Cancer-Related Neuropathic Pain

Statements	N	Degree of Agreement					
		1	2	3	4	5	Median
51. Collaboration between the pain unit and the medical oncology unit seems appropriate to address cancer pain.	75	5 (6,7%)	2 (2,7%)	6 (8,0%)	11 (14,7%)	51 (68,0%)	5
52. Specific training is required to treat patients with cancer pain.	77	1 (1,3%)	4 (5,2%)	4 (5,2%)	15 (19,5%)	53 (68,8%)	5
53. More time to properly care for patients with cancer pain is required.	75	0 (0,0%)	1 (1,3%)	3 (4,0%)	16 (21,3%)	55 (73,3%)	5
54. I am prepared to take care of patients with cancer pain.	76	2 (2,6%)	3 (3,9%)	6 (7,9%)	30 (39,5%)	35 (46,1%)	4
55. The facilities of my hospital do not guarantee a correct approach to patients with cancer pain that I attend.	72	11 (15,3%)	18 (25,0%)	3 (4,2%)	27 (37,5%)*	13 (18,1%)*	4*
56. Referral protocols should be performed for patients with cancer-related neuropathic cancer pain between pain units and medical oncology units.	75	5 (6,7%)	2 (2,7%)	6 (8,0%)	24 (32,0%)	38 (50,7%)	5

Note: *Items with lack of consensus.

neuropathic pain. In a recent systematic review, the raw prevalence of CRNP in 29 observational studies was 31%, whereas when evaluated in a survey among 137 physicians working in 50 Italian centers of palliative care reported in the same communication, the prevalence was 44%.[3] In our study, we did not evaluate the perception of the respondents on

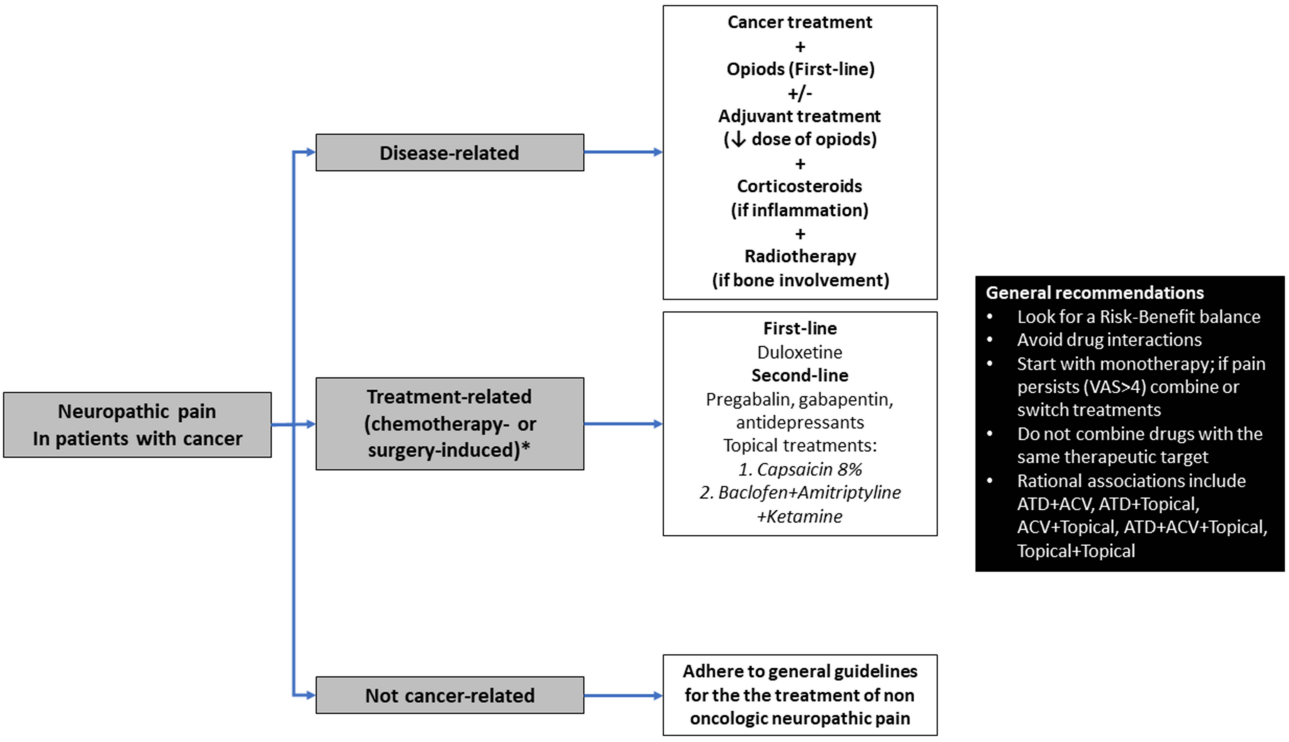

Figure 1 Treatment algorithm for cancer-related neuropathic pain. *Isolated radiotherapy-induced neuropathic pain is uncommon and could be managed in a similar way to chemotherapy- or surgery-induced neuropathic pain.
Abbreviations: ACV, anticonvulsant; ATD, antidepressant; VAS, visual analog scale.

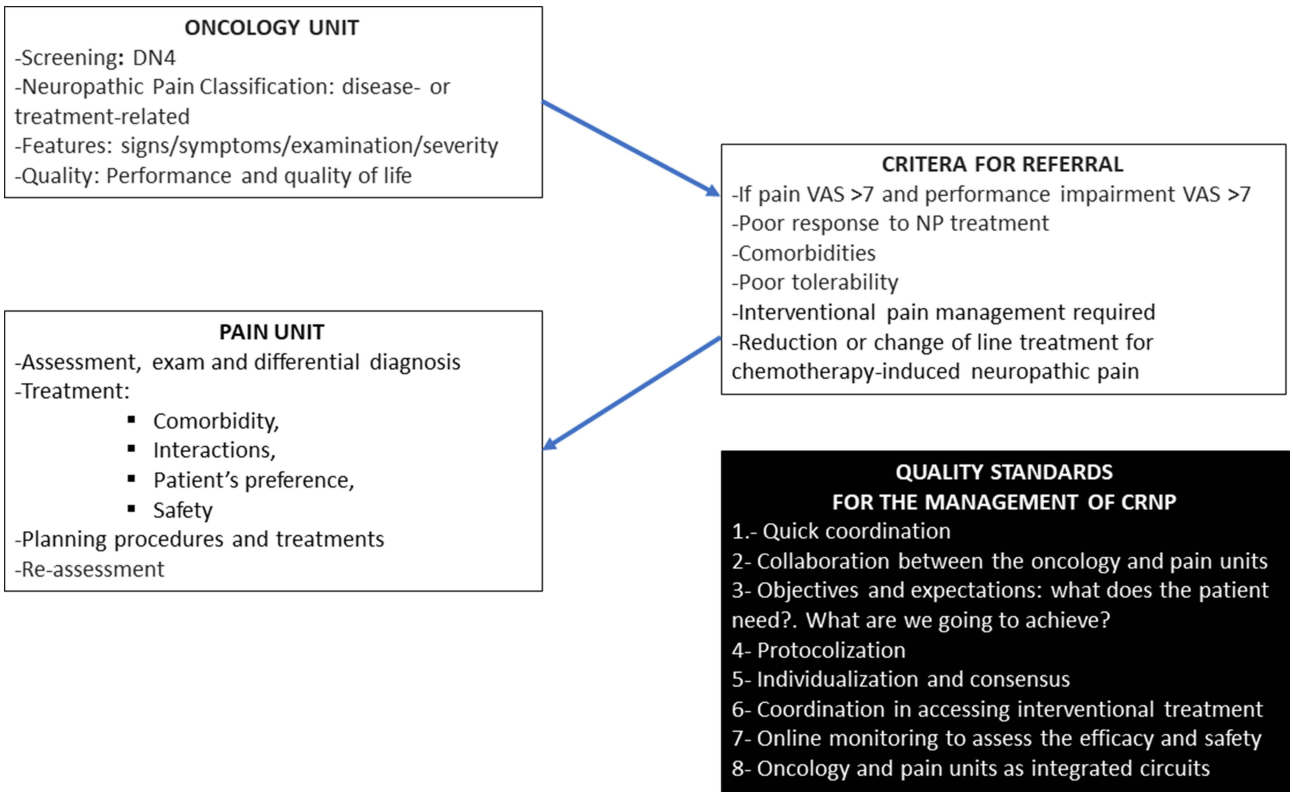

Figure 2 Recommended patient flow for the multidisciplinary management of cancer-related neuropathic pain.
Abbreviations: DN4, Douleur Neuropathique [Neuropathic Pain]-4 items; VAS, visual analog scale.

the prevalence of CRNP; however, it is likely they considered it higher than what is reported in the literature. In any case, according to a systematic review, the prevalence of neuropathic pain in patients with cancer varies from 19% to 39% when including patients with mixed pain.[2] On the other hand, in many cases, cancer is a long-lasting disease, and the prevalence of CRNP may differ substantially during the course of the disease, from the initial diagnosis through the treatment and finally in patients who survive or, on the contrary, require palliative care. In our view, further studies on the prevalence of CRNP throughout the course of the disease are needed.

The perceptions of specialists from palliative care on the frequency and impact of CRNP differs from that of other specialists, with a higher frequency of patients with CRNP, a higher frequency of moderate to severe pain and a greater impact on the quality of life and mood. These results are consistent with other studies on cancer pain. A study evaluating the prevalence and impact of breakthrough pain and its impact among patients with cancer found the highest prevalence among patients treated in palliative care units.[24] In a study conducted of 156 patients with cancer, the authors reported that those with neuropathic pain hospitalized in the palliative care unit showed greater severity of symptoms of fatigue and depression than those hospitalized in general wards.[25]

A high degree of consensus was reached for all statements concerning the assessment and diagnosis of CRNP. However, it is interesting to note that whereas 80% of the respondents agreed that ascertaining the presence of neuropathic pain is not easy because of the lack of standardized tools, 14% disagreed with this notion. Possibly the more rigorous tool for diagnosing neuropathic pain is the grading system proposed by the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain, which, using information from the history, clinical examination and confirmatory tests, categorized pain as possible, probable and definite.[26] Previous criteria of the NeuPSIG have been adapted for cancer patients through a consensus process,[27] but we are not aware of attempts to adapt the 2016 updated criteria. In fact, the NeuPSIG criteria have not been widely adopted, as their reliability and applicability in clinical practice have not been established.[10] The DN4 (Douleur Neuropathique [Neuropathic Pain]-4 items), Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and painDETECT

(PDQ) are screening tools for neuropathic pain that have shown good accuracy in patients with cancer; it is believed that until the standardization of clinical diagnosis for CRNP is validated, these tools may be useful in clinical practice to identify potential cases of CRNP.[11] This situation is consistent with the agreement of most respondents in our survey, indicating that there are no standardized diagnostic tools for NP diagnosis.

Regarding specific syndromes, the only statement with a lack of consensus was the following: "Of breast cancer patients undergoing RT treatment, 21–65% will develop chronic NP", which was based on a literature review on CRNP.[28] The development of neuropathic pain after the diagnosis of breast cancer is frequent (over 30% of the patients during the first year after diagnosis), and anxiety, arm symptoms, Stage III/IV cancer, breast-conserving surgery with axillary lymph node dissection, mastectomy with axillary lymph node dissection and damage to the intercostobrachial nerve have been identified as risk factors for the occurrence of neuropathic pain.[29] The prevalence of CRNP is higher after treatment; thus, in a systematic review, Ilhan et al[30] reported that among patients with breast cancer who reported pain after treatment, the estimated prevalence of neuropathic pain ranged from 33% to 58% using screening questionnaires and from 30% to 57% using NeuPSIG criteria; however, this systematic review does not specify figures for radiotherapy. It is possible that our lack of consensus reflects to some extent a lack of information on this topic. Other authors have reported that radiotherapy-induced neuropathic pain has scarcely been investigated.[31]

There were some disagreements regarding the multidisciplinary approach and referral criteria for the management of neuropathic pain. Thus, there was no consensus on the statement "current hospital facilities do not guarantee a correct approach to patients with cancer pain", especially among medical oncologists. The lack of consensus among respondents from oncology radiotherapy with the statement "a collaboration between the Pain Unit and the Medical Oncology Unit seems appropriate to address cancer pain" is likely a consequence of not being one of the specialties involved in the statement. Interestingly, although all specialists reached consensus that they were prepared to take care of patients with cancer pain, respondents from pain units showed the lowest degree of agreement; we think that this finding suggests a perception of greatest need for a multidisciplinary approach from the perspective of the pain physician, a hypothesis that is supported by the fact that 100% of pain physicians agreed that "collaboration between the Pain Unit and the Medical Oncology Unit seems appropriate to address cancer pain". Overall, we believe that these disagreements reflect the lack of a multidisciplinary and holistic approach to the management of CRNP, an approach that, in our view, should be promoted by the specialties involved.

Conclusions

Our main conclusions are as follows:

1. There was a high degree of consensus on statements related to the prevalence and impact of CRNP among specialists.
2. By consensus, the pathophysiology of CRNP is considered to be complex and largely unknown and coexists with other pathologies.
3. It is important to determine the etiology of neuropathic cancer pain because its management differs depending on whether it is disease-related or treatment-related.
4. Neuropathic cancer pain assessment and diagnosis are not easy, as there are no standard tools to diagnose this type of pain. However, there is consistency between clinical diagnosis and the results of screening tools, such as LANSS and DN-4.
5. Neuropathic cancer pain prevention and early recognition are crucial to avoid serious and disabling forms, and for this purpose, it is essential to avoid or decrease neurotoxic events after cancer treatment and to determine the predictive factors of neuropathic cancer pain (female sex, youth, increased body mass index, more advanced cancer stage, perineural invasion, chemotherapy or invasive surgeries, genetic polymorphisms associated with increased pain sensitivity, depression, anxiety, stress, sleep disorders, low socioeconomic level, multifocal pain and intensity of perioperative pain).

6. Chemotherapy-induced neuropathic pain is a limiting factor in cancer treatment. It is often underreported, underdiagnosed and undertreated. It can cause delays in the administration of a new cycle, reduction of cycle doses or even decreased therapy.
7. Chemotherapy-induced neuropathic pain has a high prevalence early (first months) in treatment, and in almost 30% of patients, it becomes chronic (> 6 m); it is especially frequent in head and neck, gynecological, gastrointestinal, lung and urogenital tumors. Taxanes and vinca alkaloids frequently produce persistent polyneuropathy.
8. There is no clear consensus on first-line treatment, which is a challenge for clinicians and patients. Duloxetine is a treatment that has shown sufficient evidence to recommend its use in oxaliplatin-related chemotherapy-induced neuropathic pain.
9. Regarding new treatments, there are advances in topical treatments with baclofen + amitriptyline + ketamine, menthol and capsaicin 8%, the last one as a disease-modifying drug. There are also systemic drugs, such as angiotensin-II receptor antagonists and Toll-like receptor 4 (TLR4) receptor inhibitors.
10. Collaborative work between pain and oncology units is recommended when addressing cancer-related pain, especially in patients with significant pain severity or decreased performance as well as those who would benefit from interventional pain management.

Abbreviations

CINP, chemotherapy-induced neuropathic pain; CRNP, cancer-related neuropathic pain, DN4, Douleur Neuropathique [Neuropathic Pain]-4 items; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; NeuPSIG, Special Interest Group on Neuropathic Pain; PDQ, painDETECT; SD, standard deviation.

Data Sharing Statement

All data are presented in the manuscript.

Ethics Approval and Informed Consent

The study was revised and approved by the Ethics Committee of the University Hospital "La Princesa" (Madrid, Spain). The study did not include patients but instead was a survey among physicians; therefore, informed consent was not required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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