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ORIGINAL ARTICLE

A cross-sectional, comparative, syndromic description of oncological mixed pain in Medical Oncology units in Spain

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Abstract

Objective The reason cancer pain remains prevalent and hard to classify may be partially explained by the failure to identify neuropathic mechanisms. The objective of this research was to identify the syndromes of cancer pain that may be particularly hard to manage due to their mixed pathophysiology.

Design A series of 384 patients who had cancer of any type, at any stage, and suffered from chronic pain (symptom onset > 3 months) were assessed during a routine return visit in Spain. Medical oncologists indicated the presence and pathophysiology of 33 predefined pain syndromes on a per-patient basis. This information was then measured against clinical, psychosocial, and health care-related data to determine which syndromes pose particular challenges.

Results The mean (standard deviation) age of patients was 61.6 (12.6) years, 49.7% were women. Most (82%) had advanced metastatic disease, 68.7% were on second-line or palliative therapies. The worst syndrome was nociceptive, pure neuropathic, and mixed in 34.6, 26.9, and 38.6% of patients, respectively. Any syndrome could be of mixed pathophysiology. Only 10 syndromes were common (≥ 5% of patients). Syndromes related to malignant bone pain and involvement of chest wall structures were the most frequent. Certain syndromes (including tumor-related bone pain, chemotherapy-induced peripheral neuropathies, paraneoplastic pain syndromes, and malignant neuralgias or injury to cranial nerves) can be particularly challenging when they have a mixed pathophysiology, because the neuropathic component is rarely or unevenly considered.

Conclusions Virtually all cancer pain syndromes can present mixed pathophysiology. Certain syndromes can include neuropathic components that are frequently overlooked.

Keywords Cancer · Classification · Chronic pain · Neoplasms · Neuralgia · Pathophysiology

Introduction

Pain is one of the most feared symptoms of cancer [1]. Many cancer patients have pain [2], which usually complicates their clinical condition. Cancer pain can pose relevant diagnostic and therapeutic challenges [3], as some patients have complex pain syndromes and fail to obtain satisfactory pain control [4]. In order to facilitate the task of identifying challenging cancer pain

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conditions in the clinical practice, a taxonomy or classification system for cancer pain has been largely pursued, and several systems have been produced [5]. However, a consensus on the content and structure has not yet been reached [6, 7].

One of the reasons cited for the difficulties in obtaining adequate control of cancer pain is the failure to identify and effectively treat neuropathic mechanisms [8]. Pain pathophysiology is, in fact, one of the core domains that have been recommended for use in formal classification systems [5, 9]. An example of this would be the Edmonton Classification System for cancer pain (ECS-CP), which is the only system that has undergone extensive validation [4]. During the development of the ECS-CP, the presence of a neuropathic component was found to correlate with the complexity of pain management [4].

The epidemiology of neuropathic pain in cancer patients has been studied in less detail than in non-cancer patients [10]. The pathophysiology of neuropathic cancer pain can be different from neuropathic non-cancer pain [11]; the pain related to tumoral growth frequently encompasses both nociceptive and neuropathic mechanisms to form a mixed pain mechanism [12, 13]. Precisely, in these cases, the neuropathic component can be hard to identify [12].

There has been a call to collect empirical data to refine cancer pain classification [5]. On these grounds, we performed this research to provide empirical evidence of the presence and related difficulties mixed cancer pain poses in clinical practice. As a novelty, we adopted a syndromic approach to describe pain. While this approach is too tedious for routine practice, it can be adopted in research settings to relate clinical features with pathophysiology [14, 15]. The type of pain has been related to cancer pain response [16]. The objective was to identify pain syndromes that are more likely to present a mixed pathophysiology and consequently cause diagnostic or therapeutic issues.

Methods

Study design, setting, and participants

This research was a nationwide cross-sectional, non-interventional study. The investigators were 93 medical oncologists with experience in the management of cancer and cancer pain. Medical oncologists receive formal training on pain management (including clinical rotations and accredited courses) during their internship as resident physicians in Spain. Participants were in- or out-patients who had cancer of any type, at any stage, who suffered from chronic pain (symptom onset longer than 3 months [17]), and who received care at the premises of any Medical Oncology unit. The investigators were responsible for the medical care of the oncologic condition of study participants.

Assessments and procedures

All data were collected in a single visit. Basic sociodemographic data and information about cancer was recorded, including date of diagnosis, Karnofsky score, anatomical location of the primary tumor, stage and status of the disease, presence and location of metastases, and history of neurotoxic chemotherapy.

A checklist of pain syndromes was developed to structure data capture. Based on previous descriptions [15, 18], one of the authors (JV) prepared an initial proposal that included 64 syndromes. This list was subsequently simplified and refined during two discussion rounds with another two authors (AE and AL). The final version included 23 tumor-related pain syndromes and 10 cancer treatment-related pain syndromes plus an open field labelled "other" (Online Resource 1). For each syndrome, checkboxes were included to specify its pathophysiology as either nociceptive or neuropathic (in cases of mixed pathophysiology, both options had to be checked) and, for neuropathic syndromes, whether the diagnosis was done following the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain criteria or following other criteria. Whenever the NeuPSIG criteria were used, the level of diagnostic certainty (1 to 4) attained for the neuropathic component had to be consigned. Investigators were instructed to check as many syndromes as necessary to fully describe the pain symptoms of the patient. When more than one syndrome was reported, the investigators were asked to state the syndrome that caused the worst pain symptoms—the one that caused more morbidity, disability, or risk for the patient's health. Aside from this checklist, investigators were also asked to provide a global appraisal of the patient's pain pathophysiology either as purely nociceptive, purely neuropathic, or mixed.

Study groups were defined according to the pain pathophysiology: nociceptive, neuropathic, or mixed. Two alternative definitions were used, one based on the aforesaid global appraisal of patients' pain pathophysiology (definition A) and another based on the pathophysiology assigned to the syndrome that caused the worst pain symptoms (definition B). These two perspectives are important for patients who endure pain in more than one location, as oncologic patients frequently do, since pain located at different areas may involve distinct mechanisms and involve a combination of pain with and without neuropathic characteristics [19]. This distinction is subtle but important, because there is still no consensus as to whether the term "mixed" should be reserved for conditions in which different pathophysiological mechanisms coalesce to produce a consistent pain syndrome or whether it can be more widely used in patients with distinct conditions, one featuring pure neuropathic and the other pure nociceptive mechanisms [8].

The presence of breakthrough pain and of sensory deficits in any area of pain was checked, as well. Investigators were also asked to report on the diagnostic work-up followed for

the patient's pain. For this purpose, they had to select from a separate dedicated checklist of common diagnostic procedures (including neurologic examination, non-quantitative and quantitative sensory testing, imaging, neurophysiological tests, pain scales, skin biopsy, and therapeutic assays). Another checklist of some common concomitant diseases was presented to investigators where they could record patients' comorbidities. We also addressed some health care-related factors that could potentially influence the experience, diagnosis, or treatment of chronic pain. These factors included barriers to adequate pain management or risk factors for undertreatment of pain, perceived difficulties for the management of pain, a psychosocial evaluation of the patient, and a list of health professionals who had participated in patient's pain management. This information on health care-related factors was subjectively appraised by the investigators after interviewing the patients and gathering information from their medical files.

In addition, some clinical tools were administered to patients. The *Douleur Neuropathique in 4 questions* (DN4) [20], a recognized screening tool for neuropathic pain, was used to test its diagnostic performance in cancer patients. The abbreviated form of the Brief Pain Inventory (BPI) [21] was used to obtain measures of pain severity and interference with daily activities. Lastly, health-related quality of life measures were obtained using the EuroQoL 5-Dimensions [22, 23].

A thorough description and ranking of the syndromes that feature at least one neuropathic component was carried out based on factors that usually complicate pain management precisely because of this neuropathic component. This description included how often (a) the syndrome occurred, (b) entailed mixed pain mechanisms, (c) was the origin of the worst pain symptoms, (d) was it associated with breakthrough pain, (e) the neuropathic component was not probable or definite in the NeuPSIG criteria, (f) the global pain pathophysiology was not declared mixed despite the syndrome being considered to have mixed pathophysiology, and (g) specific diagnostic tests for neuropathic pain were not used.

Statistical methods

All analyses were conducted using observed data. Test units were patients for most analyses, except for the frequencies of individual syndromes. Appropriate summary statistics were used to describe the study variables in each study group. Since the study groups were defined in two alternative ways, all analyses were done in duplicate, one series for each definition. Inferences to the source population were done by calculating the 95% confidence intervals (CIs) of descriptive statistics. Non-overlapping CIs were regarded as statistically significant differences.

Risk scores for both pure neuropathic and mixed pain syndromes were calculated as the average of the frequencies of the factors expected to complicate the management of pain (see above).

All analyses were implemented with the statistical package SAS (version 9.1.3; SAS Institute Inc. Cary, NC, USA).

No formal sample size calculation was performed. The number of patients available was expected to be high enough to estimate several proportions and calculate a multiple linear regression model.

Results

Distribution and characteristics of patients

Data from 598 patients from 49 sites was received; 214 patients (35.8%) were excluded from the analyses, mostly (206 patients) because they did not have chronic pain (i.e., the time since pain onset was shorter than 3 months). Of the 384 patients remaining, 107 (27.9%) had nociceptive pain, 12 (3.1%) neuropathic pain, and 265 (69.0%) mixed pain according to definition A. Definition B was applied to 350 patients. According to this assignment, 121 (34.6%) had nociceptive pain, 94 (26.9%) neuropathic pain, and 135 (38.6%) mixed pain. In total, 717 pain syndromes were reported. There was moderate to good agreement between both classifications (weighted kappa = 0.662). The pathophysiology was known for 688 syndromes, of which 290 (42.2%) were nociceptive, 179 (26.0%) neuropathic, and 219 (31.8%) mixed.

Tables 1 and 2 show the characteristics of patients, cancer, and pain. The mean Karnofsky performance status was significantly lower in patients with mixed pain than in patients with nociceptive pain grouped as per the definition A. The most frequent locations of the primary tumor were the lungs (20.8% of patients), the breasts (19.8%), and the colon/rectum (15.4%). Mixed pain was noted in all cancer locations (including those not listed in Table 1). Many patients (81.8%) had advanced (stage IV) cancer. The prevalence of concomitant diseases was similar in all study groups. Advanced cancer stages were significantly less common in patients with mixed pain as per definition B. Most patients (53.5%) were on second or successive lines of therapy. In total, 76.3% had received at least one neurotoxic chemotherapeutic agent.

The proportion of patients with breakthrough pain episodes (260 out of 380, 68.4%) did not differ significantly between study groups. Conversely, the proportion of patients with sensory deficits in any area of pain (86 out of 382, 22.5%) was significantly lower in patients with nociceptive pain than in other patients (Table 2). The pain was related to the growth of the primary tumor or its metastases in 295 out of 384 patients (76.8%), to anti-cancer therapies in 28 patients (7.3%), to both factors in 50 patients (13.0%), and unrelated to cancer in the remaining 11. Pain related to tumoral growth was significantly more frequent in patients with nociceptive pain (Table 2). The

Table 1 Characteristics of patients and cancer

	Definition A: global appraisal of pain pathophysiology			Definition B: pathophysiology of the "worst" syndrome		
	Nociceptive (*N* = 107)	Neuropathic (*N* = 12)	Mixed (*N* = 265)	Nociceptive (*N* = 121)	Neuropathic (*N* = 94)	Mixed (*N* = 135)
Age (years) [mean (SD)]	63.3 (12.3)	66.8 (13.0)	60.7 (12.7)	62.7 (12.4)	61.8 (13.1)	60.1 (12.8)
Proportion of women [*n* (%)]	55 (52.4)	9 (75.0)	126 (47.6)	60 (50.0)	52 (55.3)	62 (45.9)
Time since cancer diagnosis (months) [mean (SD)]	40.1 (55.9)	46.6 (29.7)	35.1 (44.5)	42.8 (54.2)	35.1 (45.8)	30.4 (39.9)
Karnofsky performance score (points) [mean (SD)]	81.2 (13.7)*	75.5 (8.2)	76.2 (14.6)*	79.9 (14.7)	75.6 (14.6)	77.8 (13.8)
Location of primary tumor [*n* (%)][a]						
Lung	27 (25.2)	0 (0.0)	53 (20.0)	27 (22.3)	18 (19.1)	27 (20.0)
Breast	24 (22.4)	4 (33.3)	48 (18.1)	27 (22.3)	24 (25.5)	18 (13.3)
Colon/rectum	13 (12.2)	3 (25.0)	43 (16.2)	12 (9.9)	12 (12.8)	31 (23.0)
Pancreas	4 (3.7)	0 (0.0)	24 (9.1)	7 (5.8)	6 (6.4)	12 (8.9)
Prostate	9 (8.4)	0 (0.0)	18 (6.8)	11 (9.1)	3 (3.2)	8 (5.9)
Head/neck	3 (2.8)	1 (8.3)	19 (7.2)	7 (5.8)	8 (8.5)	7 (5.2)
Kidney/bladder	10 (9.4)	0 (0.0)	9 (3.4)	10 (8.3)	2 (2.1)	7 (5.2)
Stage of the disease [*n* (%)]						
I	0 (0.0)*	1 (8.3)*	10 (3.8)*	0 (0.0)*	2 (2.1)*	6 (4.5)*
II	2 (1.9)*	2 (16.7)*	12 (4.6)*	4 (3.4)*	4 (4.3)*	5 (3.7)
III	14 (13.6)*	2 (16.7)*	26 (9.9)*	14 (11.9)*	10 (10.6)	14 (10.5)
IV	87 (84.5)*	7 (58.3)*	216 (81.8)*	100 (84.8)*	78 (83.0)*	109 (81.3)*
Presence of concomitant diseases (%)	67 (62.6)	5 (41.7)	161 (61.0)	73 (60.3)	56 (60.2)	86 (63.7)

The asterisks denote significant differences between the study groups (see the confidence intervals in the Online Resource 2). All the descriptions have been made using observed data; the denominators used to calculate relative frequencies might be lower than the column totals

NP neuropathic pain, *SD* standard deviation

[a] Only the locations present in at least 5% of patients are listed. In total, up to 28 different locations were declared

pain intensity was higher in the mixed pain group than in the other study groups, although the difference did not reach statistical significance (Table 2). The difference of maximal (worst) and average pain intensity between the mixed and neuropathic pain groups as per definition B was almost significant (Online Resource 3).

Nearly all patients (98.1%) were receiving medications for pain, mostly opioids (82.9% of patients), followed by antiepileptic agents (29.4%), paracetamol (27.5%), propionic acid derivatives (25.4%), and pyrazolones (24.1%). The proportion of patients on opioids was significantly greater in the mixed pain group than in the nociceptive pain group as per definition A (Table 2).

Health care-related data

The pain was managed by a single physician in most patients (233 out of 383, 60.8%). In almost one-third (121 patients, 31.6%), two physicians participated. In many patients (342 out of 384, 89.1%), the oncologist was the main responsible for the management of pain. A minority of patients (57 out of 383, 14.9%) were receiving care at pain clinics.

The presence of barriers to adequate pain management was reported in few patients (26 out of 383, 6.8%). Perceived difficulties for the management of pain were reported in 95 out of 382 patients (24.9%). The perceived lack of resources for the evaluation of pain was significantly more frequent in patients with pure neuropathic pain than in patients with mixed pain (definition B, Table 3). The most frequent difficulty in the mixed pain group (either definition) was the lack of efficacy of analgesic therapies (Table 3).

Most patients had received a neurological examination or imaging tests (89.5%). However, some diagnostic tests specific for neuropathic pain, such as neurophysiological studies or non-quantitative sensory testing, were more frequent in the neuropathic pain group (16.7 and 33.3%, respectively, using definition A) than in the mixed pain group (6.9 and 23.3%, respectively, using definition A). These differences did not reach statistical significance.

Pain syndromes

Most patients presented only one (43.5%) or two (32.0%) pain syndromes. The number of pain syndromes per patient was

Table 2 Characteristics of pain

	Definition A: global appraisal of pain pathophysiology			Definition B: pathophysiology of the "worst" syndrome		
	Nociceptive (*N* = 107)	Neuropathic (*N* = 12)	Mixed (*N* = 265)	Nociceptive (*N* = 121)	Neuropathic (*N* = 94)	Mixed (*N* = 135)
Time since pain onset (months) [mean (SD)]	15.3 (19.1)	24.7 (26.3)	16.8 (28.6)	15.6 (19.1)	20.7 (37.2)	13.6 (18.6)
NeuPSIG level of diagnostic certainty for NP [*n* (%)][a]						
1	–[b]	0 (0.0)*	23 (9.6)*	2 (8.7)	6 (7.3)	10 (8.3)
2	–[b]	1 (12.5)*	48 (20.0)*	7 (30.4)*	7 (8.5)*	33 (27.3)*
3	–[b]	2 (25.0)*	86 (35.8)*	6 (26.1)	24 (29.3)	48 (39.7)
4	–[b]	5 (62.5)*	83 (34.6)*	8 (34.8)*	45 (54.9)*	30 (24.8)*
Presence of breakthrough pain [*n* (%)]	63 (60.0)	8 (66.7)	189 (71.9)	73 (60.8)	76 (80.9)	94 (70.1)
Presence of sensory deficits in any area of pain [*n* (%)]	7 (6.5)*	5 (41.7)	74 (28.1)	17 (14.1)*	33 (35.1)*	30 (22.4)
Relationship of pain with cancer [*n* (%)]						
Pain related to tumoral growth	92 (86.0)*	5 (41.7)*	198 (74.7)*	98 (81.0)*	70 (74.5)*	105 (77.8)*
Pain related to anti-cancer therapies	6 (5.6)	4 (33.3)*	18 (6.8)	4 (3.3)*	6 (6.4)	11 (8.1)
Pain related to tumoral growth and anti-cancer therapies	7 (6.5)*	0 (0.0)*	43 (16.2)*	15 (12.4)	16 (17.0)*	16 (11.9)
Pain not related to cancer	2 (1.9)	3 (25.0)*	6 (2.3)	4 (3.3)	2 (2.1)	3 (2.2)
Brief Pain Inventory scores (points) [mean (SD)]						
Worst 24 h pain intensity (points	6.6 (2.4)	6.6 (2.5)	6.7 (2.4)	6.7 (2.4)	6.2 (2.5)	7.0 (2.3)
Least 24 h pain intensity (points)	2.2 (1.9)	2.4 (1.7)	2.6 (2.2)	2.4 (2.1)	2.5 (2.1)	2.6 (2.3)
Average 24 h pain intensity (points)	4.2 (2.0)	4.3 (1.5)	4.5 (2.3)	4.4 (2.1)	4.1 (2.4)	4.8 (2.1)
Current pain intensity (points)	3.3 (2.4)	3.3 (1.4)	3.6 (2.7)	3.5 (2.6)	3.4 (2.6)	3.7 (2.7)
Pain interference score (points)	5.2 (2.7)	4.7 (2.9)	5.3 (2.4)	5.2 (2.7)	5.1 (2.4)	5.4 (2.4)
DN4 total score (points) [mean (SD)]	1.5 (1.5)*	4.9 (2.5)	3.7 (2.1)	2.0 (1.7)*	4.3 (2.0)*	3.4 (2.2)*
Possible NP according to the DN4 (total score ≥ 4) [*n* (%)]	10 (9.4)*	7 (58.3)	122 (49.8)	19 (16.1)*	54 (60.7)	55 (44.7)
Opioid therapy [*n* (%)]	77 (73.3)*	10 (90.1)	223 (86.4)*	92 (77.3)	76 (87.4)	115 (85.8)
Treatment with antiepileptic agents [*n* (%)]	9 (8.6)*	7 (63.6)	94 (36.4)	15 (12.6)*	39 (44.8)	45 (33.6)
Participation of pain clinics in pain management [*n* (%)]	8 (7.6)	3 (25.0)	46 (17.4)	14 (11.6)	21 (22.3)	18 (13.3)

The asterisks denote significant differences between the study groups (see the confidence intervals in the Online Resource 3). All the descriptions have been made using observed data; the denominators used to calculate relative frequencies might be lower than the column totals

BPI Brief Pain Inventory, *DN4 Douleur Neuropathique in 4 questions*, *NP* neuropathic pain, *SD* standard deviation

[a] Calculated within the subgroup of patients in whom the NeuPSIG criteria were used (95% of patients with either pure neuropathic or mixed pain)

[b] This information was not requested when the global appraisal of the patient's pain pathophysiology was nociceptive

similar in all study groups (data not shown). Only 10 syndromes affected ≥ 5% of patients. The most frequent syndromes involved the infiltration of bones: vertebrae, sacrum, pelvis, hip, or long bones (Fig. 1). Among the top 10 syndromes, one (chemotherapy-induced peripheral neuropathy) was related to anti-cancer therapy. Within the mixed pain group, chronic post-mastectomy pain, pain due to malignant chronic intestinal (semi)obstruction, and pain following other surgeries also affected ≥ 5% of patients. There were cases of mixed pain in all pain syndromes. Furthermore, some uncommon syndromes (such as malignant chronic headache or esophageal mediastinal pain) were only reported in patients with mixed pain. The pain from metastases in long bones was mainly classified as nociceptive, post-mastectomy pain as neuropathic, and both painful malignant radiculopathy and chronic intestinal (semi)obstruction as mixed. Painful chemotherapy-induced peripheral neuropathy, malignant plexopathy, peripheral neuropathies, and the base of skull syndrome were rarely nociceptive (Fig. 1). The top seven syndromes in order of frequency were also those that caused the worst pain symptoms in ≥ 5% of patients. In a subset of less common syndromes that nevertheless caused the worst pain symptoms in a number of patients (base of skull syndrome, chronic otalgia or eye pain, chemotherapy-induced peripheral neuropathy, malignant plexopathy, and post-mastectomy pain), the pathophysiology was almost exclusively neuropathic or mixed (Fig. 1).

The NeuPSIG criteria were used in 95.0% of patients with any (pure or mixed) neuropathic pain, but level 3 (probable) of diagnostic certainty was not reached in up to 29.0% of them. Remarkably, the proportion of patients in whom the

Table 3 Health care-related factors and health-related quality of life

	Definition A: global appraisal of pain pathophysiology			Definition B: pathophysiology of the "worst" syndrome		
	Nociceptive (*N* = 107)	Neuropathic (*N* = 12)	Mixed (*N* = 265)	Nociceptive (*N* = 121)	Neuropathic (*N* = 94)	Mixed (*N* = 135)
Presence of barriers for adequate pain management [*n* (%)]	6 (5.6)	0 (0.0)	20 (7.6)	9 (7.4)	5 (5.4)	7 (5.2)
Presence of perceived difficulties for pain mgmt. [*n* (%)]						
Any difficulty	21 (19.8)	3 (25.0)	71 (26.9)	29 (24.0)	24 (25.5)	34 (25.4)
Lack of efficacy of analgesic therapies	6 (5.7)	2 (16.7)	37 (14.0)	9 (7.4)	10 (10.6)	24 (17.9)
Lack of adherence to analgesic therapies	12 (11.3)	0 (0.0)	20 (7.6)	14 (11.6)	7 (7.4)	9 (6.7)
Insufficient resources for the evaluation of pain	6 (5.7)	1 (8.3)	17 (6.4)	8 (6.6)	11 (11.7)*	2 (1.5)*
Incomplete acknowledgment of pain pathophysiology	2 (1.9)	0 (0.0)	4 (1.5)	2 (1.7)	3 (3.2)	0 (0.0)
Insufficient knowledge/training for pain evaluation or treatment	1 (0.9)	0 (0.0)	1 (0.4)	1 (0.8)	1 (1.1)	0 (0.0)
Insufficient resources for the treatment of pain	1 (0.9)	0 (0.0)	1 (0.4)	1 (0.8)	0 (0.0)	1 (0.7)
Presence of adverse psychosocial factors [*n* (%)]	43 (40.6)	5 (41.7)	132 (50.0)	47 (39.2)	49 (52.1)	64 (47.8)
EQ-5D index score [mean (SD)][a]	0.54 (0.27)	0.59 (0.26)	0.51 (0.26)	0.54 (0.27)	0.56 (0.23)	0.49 (0.27)
EQ-5D VAS score [mean (SD)][b]	58.3 (20.1)	67.1 (15.4)	55.1 (20.4)	57.0 (20.4)	58.7 (17.9)	53.9 (21.5)

The asterisks denote significant differences between the study groups (see the confidence intervals in the Online Resource 4). All the descriptions have been made using observed data; the denominators used to calculate relative frequencies might be lower than the column totals

EQ-5D EuroQoL 5-Dimensions, *SD* standard deviation, *VAS* visual analogue scale

[a] Preference-based quantitative measure of the patient's health status obtained with the scoring formula for the Spanish population (range = 0–1). Higher scores indicate better quality of life

[b] Global measure of well-being elicited against an explicit comparative standard on a VAS (range = 0–100). Higher scores indicate better quality of life

neuropathic component was confirmed (level 4) was significantly lower in the mixed pain group than in the neuropathic pain group (Tables 2 and 4). The penetration of NeuPSIG criteria was variable across syndromes (Table 4).

In general, the global appraisal of patients' pain pathophysiology matched the pathophysiology declared for nociceptive and neuropathic syndromes but not for mixed pain syndromes (Table 4). Among these unmatched syndromes, the pain from metastases in long bones, from the infiltration of the pelvis or hips, and malignant chest wall pain stood out because of their high prevalence.

Among the syndromes with the highest mixed pain risk score, two were also very common in this series of patients: the infiltration of vertebrae or the sacrum and the metastases in long bones (Table 4). Strikingly, the correspondence with the general pain pathophysiology of metastases in long bones was very low when the pathophysiology of the syndrome itself was mixed but not purely neuropathic. It is also worth noting that three syndromes that posed abdominal pain (malignant hepatic distension/splenomegaly, the retroperitoneal syndrome, and malignant chronic intestinal semi-obstruction) also had a high mixed pain risk score (Table 4). Interestingly, the average mixed pain risk score (47.6) was higher than the average neuropathic pain risk score (39.8, calculations not shown). So, although both types of pain involved neuropathic mechanisms, there were more factors that could complicate the management of pain in the mixed than in the pure neuropathic pain syndromes.

DN4

As expected, the mean total score was significantly lower in the nociceptive pain group than in the other study groups. However, the scores were higher in the neuropathic pain group than in the mixed pain group, and this difference reached statistical significance (definition B, Table 2). Only 9.4% of patients of the nociceptive pain group had a total score within the neuropathic range (90.6% specificity). The sensitivities of the tool in the groups of neuropathic and mixed pain groups (definition A) were, respectively, 58.3 and 49.8%.

Discussion

The present research has mapped information about the dimensions considered in existing cancer pain classification systems [7, 24] as well as pain and patient features that have been used to classify cancer pain [5] to a syndromic description of pain conditions. The result indicates that chronic oncologic mixed cancer pain is frequent and challenging. Virtually, all cancer pain syndromes can have a mixed pathophysiology and, compared with pure nociceptive or neuropathic syndromes, mixed cancer pain syndromes may pose greater diagnostic and therapeutic difficulties. In support of this idea, we have found lower correspondence with the global appraisal of patient's pain pathophysiology, reduced application of the

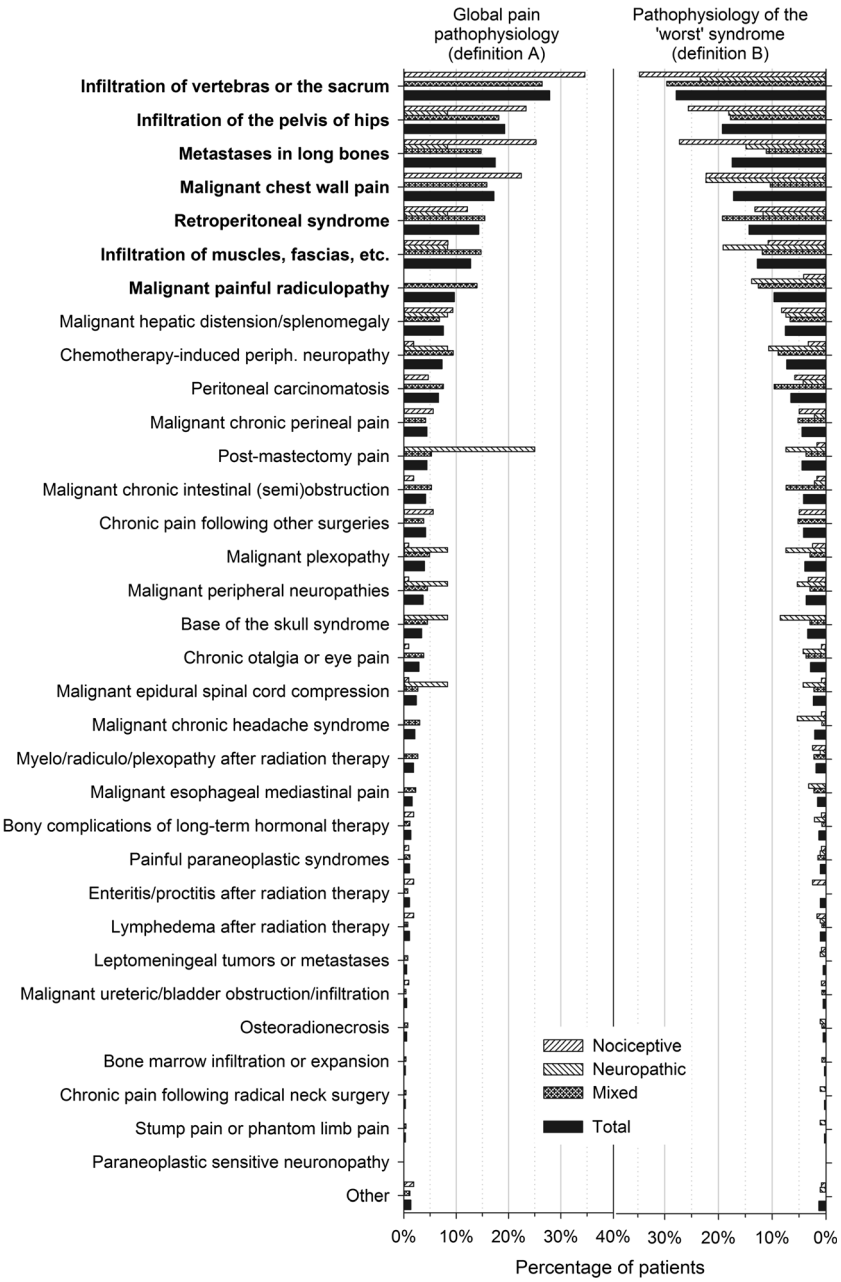

Fig. 1 Frequencies of cancer-related pain syndromes. The chart is sorted by descending order of frequency. The syndromes that caused the worst pain symptoms in at least 5% of patients are marked in bold text

NeuPSIG diagnostic criteria and diagnostic tests specific for neuropathic pain, presence of mixed pain in rare syndromes, lower referral rate to pain clinics, higher intensity of pain, and a greater consumption of opioids in patients with mixed pain syndromes.

There are specific syndromes that may be especially challenging to clinical oncologists when they have a mixed pathophysiology. Painful metastases in long bones, chemotherapy-induced peripheral neuropathy, malignant chronic hepatic distension/splenomegaly, malignant plexopathy, and the base of skull syndrome shared at least three of the aforementioned untoward factors. Also, some quite uncommon syndromes such as the painful paraneoplastic syndromes, the malignant chronic headache syndrome, and chronic otalgia/eye pain or pain from involvement of cranial nerves had the highest mixed pain risk scores. Only one in all the aforementioned syndromes was among the syndromes that caused the worst pain symptoms in at least 5% of patients. This suggests that the most problematic syndromes are not necessarily the most frequent ones, in keeping with the idea that there is only a subset of cancer patients who have pain that is particularly hard to treat [4]. Considering our results, the existence of such a subset may be partially explained by the presence of uncommon syndromes of mixed pathophysiology.

The complexity of cancer pain conditions usually requires multimodal therapies [25, 26]. However, consistently with a

Table 4 Characteristics of pain syndromes arranged in descending order according to the mixed pain risk score

	Global frequency *n* (% of 384 patients)	Mixed in (% patients)[a]	Worst pain in (% patients)[a]	NeuPSIG < 3		Correspondence with global pathophysiology[d]			Mixed pain risk score[e]
				(% mixed)[b]	(% neurop.)[c]	(% mixed)	(% neurop.)	(% nocicep.)	
Painful paraneoplastic syndromes	4 (1.0)	25.0%	75.0%	100.0%	0.0%	33.3%	–	100.0%	66.8
Malignant chronic headache syndrome	8 (2.1)	12.5%	12.5%	100.0%	50.0%	12.5%	–	–	61.6
Malignant ureteric/bladder obstruction/infiltration	2 (0.5)	50.0%	50.0%	100.0%	–	100.0%	–	100.0%	60.1
Metastases in long bones	67 (17.5)	10.4%	32.8%	71.4%	44.4%	17.9%	100.0%	85.2%	59.5
Chronic otalgia or eye pain	11 (2.9)	54.5%	72.7%	33.3%	0.0%	60.0%	–	100.0%	58.8
Malignant hepatic distension/splenomegaly	29 (7.6)	31.0%	48.3%	44.4%	0.0%	44.4%	0.0%	70.0%	56.9
Retroperitoneal syndrome	55 (14.3)	45.5%	67.3%	36.0%	27.3%	61.0%	100.0%	100.0%	55.8
Malignant plexopathy	15 (3.9)	33.3%	46.7%	40.0%	25.0%	30.8%	100.0%	0.0%	55.5
Infiltration of vertebrae or the sacrum	107 (27.9)	33.6%	53.3%	38.9%	11.8%	50.0%	–	94.6%	55.2
Malignant chronic intestinal (semi)obstruction	16 (4.2)	25.0%	37.5%	75.0%	100.0%	28.6%	–	50.0%	54.0
Malignant esophageal mediastinal pain	6 (1.6)	50.0%	66.7%	33.3%	50.0%	50.0%	–	–	53.6
Peritoneal carcinomatosis	25 (6.5)	56.0%	28.0%	50.0%	0.0%	70.0%	–	100.0%	53.1
Chemotherapy-induced peripheral neuropathy	28 (7.3)	32.1%	28.6%	22.2%	62.5%	32.0%	100.0%	50.0%	52.9
Infiltration of muscles, fascia, etc.	49 (12.8)	28.6%	57.1%	50.0%	35.7%	35.9%	100.0%	100.0%	52.7
Malignant painful radiculopathy	37 (9.6)	40.5%	54.1%	33.3%	38.1%	40.5%	–	–	52.2
Malignant chronic perineal pain	17 (4.4)	47.1%	64.7%	75.0%	0.0%	72.7%	–	100.0%	52.1
Malignant chest wall pain	66 (17.2)	21.2%	54.5%	21.4%	35.7%	31.0%	–	91.7%	51.4
Base of skull syndrome	13 (3.4)	38.5%	69.2%	40.0%	25.0%	41.7%	100.0%	–	51.1
Infiltration of the pelvis or hips	74 (19.3)	24.3%	47.3%	33.3%	16.7%	37.5%	100.0%	92.0%	50.8
Osteoradionecrosis	2 (0.5)	50.0%	0.0%	0.0%	–	50.0%	–	–	50.1
Post-mastectomy pain	17 (4.4)	35.3%	41.2%	83.3%	62.5%	42.9%	33.3%	–	49.0
Malignant peripheral neuropathies	14 (3.7)	35.7%	28.6%	20.0%	33.3%	41.7%	100.0%	0.0%	48.8
Malignant epidural spinal cord compression	9 (2.3)	22.2%	33.3%	0.0%	40.0%	28.6%	100.0%	100.0%	48.1
Chronic pain following other surgeries	16 (4.2)	37.5%	68.8%	50.0%	100.0%	60.0%	–	66.7%	46.9
Lymphedema after radiation therapy	4 (1.0)	50.0%	25.0%	50.0%	–	100.0%	–	100.0%	42.7
Enteritis/proctitis after radiation therapy	4 (1.0)	0.0%	100.0%	–	–	0.0%	–	100.0%	40.3
Stump pain or phantom limb pain	1 (0.3)	0.0%	100.0%	–	100.0%	0.0%	–	–	40.1
Myelo/radiculo/plexopathy after radiation therapy	7 (1.8)	28.6%	28.6%	0.0%	40.0%	28.6%	–	–	38.1
Bony complications of long-term hormonal therapy	5 (1.3)	0.0%	40.0%	–	0.0%	0.0%	–	100.0%	28.4
Leptomeningeal tumors or metastases	2 (0.5)	0.0%	0.0%	–	100.0%	0.0%	–	–	20.2
Bone marrow infiltration or expansion	1 (0.3)	0.0%	0.0%	–	–	0.0%	–	–	20.1
Chronic pain following radical neck surgery	1 (0.3)	0.0%	0.0%	–	–	0.0%	–	–	20.1
Paraneoplastic sensitive neuronopathy	0 (0.0)	–	–	–	–	–	–	–	–
Other	5 (1.3)	0.0%	20.0%	–	0.0%	0.0%	–	100.0%	24.4

Marked in bold text are the syndromes that were present in at least 5% of the patients

[a] The denominator is the number of patients with the syndrome

[b] The denominator is the number of syndromes with mixed pain pathophysiology

[c] The denominator is the number of syndromes with pure neuropathic pathophysiology

[d] The numerators are the number of patients in whom both, the pathophysiology of the syndrome and the global pathophysiology were either mixed, pure neuropathic, or pure nociceptive, as appropriate, and the denominators are the number of patients in whom the global pain pathophysiology was considered either mixed, pure neuropathic, or pure nociceptive, as appropriate

[e] Calculated as the average of the relative frequencies, expressed as percentages, of factors expected to complicate the management of pain because of the presence of a neuropathic component: how often the syndrome occurred, how often the pain entailed mixed pain mechanisms, how often the syndrome was the origin of the worst pain symptoms, how often was it associated with breakthrough pain, how often the neuropathic component was not at least "probable" according to the NeuPSIG criteria, how often the global pain pathophysiology was not declared mixed despite the syndrome being considered to have mixed pathophysiology, and how often specific diagnostic tests for neuropathic pain (sensory testing, neurophysiology testing, and therapeutic essays with drugs targeted for neuropathic pain) were not used

recent report [27], we found that the participation of specialists other than the medical oncologists was scarce. If more specialized input is unfeasible, increasing the awareness and skills of medical oncologists for the management of pain would seem important for improving outcomes. This would entail enhancing their ability to recognize mixed pain conditions, which oncologists appear to be less unaware of, as their more frequent citing of lack of resources when diagnosing pure neuropathic pain than mixed pain suggests. Medical oncologists could learn simple procedures to identify sensory signs indicative of a neuropathic pathophysiology, such as the use of a soft brush or a pin [12, 28]. Our results reinforce the value of negative sensory signs (deficits) for this task, as they were significantly less frequent in patients with nociceptive pain. Alternatively, the use of screening tools has been proposed to facilitate recognition [12]. However, they seem to be problematic since the observed sensitivity in this study of one of the most used tools was comparable to the relatively poor performance reported in a previous epidemiologic research in the oncology setting [29] and lower than the sensitivity obtained by pain clinicians in cancer patients [30]. There seems to also be room for improving therapies, since the use of antiepileptic agents, not to mention antidepressants, was meager in comparison with the prevalence of mixed pain and the massive use of opioids.

The pain from bone metastases deserves special attention. Infiltration of vertebrae or the sacrum and painful metastases in long bones were very frequent and mainly labelled as nociceptive, but their high mixed pain risk scores suggest that covered neuropathic components may also be present. It has been proposed that bone cancer pain usually features a neuropathic component [31]. This may warrant a rethinking of the pathophysiology, classification, and treatment of pain from bone metastases.

The authors of the ECS-CP have repeatedly shown that the presence of a neuropathic component correlates to a worse pain prognosis [4, 32]. Nonetheless, although these authors did not segregate mixed cancer pain from pure neuropathic pain conditions [24], our results support the separation of these types of pain into different categories, given that mixed pain seems to associate with more untoward outcomes. In fact, another classification system [33], and informal approaches for classifying cancer pain took mixed pain as an independent group [5]. Also, this study provides epidemiological support to the idea that the term "mixed" should be reserved for syndromes where there is coalescence of both neuropathic and nociceptive mechanisms acting simultaneously; otherwise, the prevalence of mixed pain would seem unreasonably high (69.0 vs. 38.6%, see the "Results" section). This idea is consistent with the coalescence principle that was regarded first when the concept of mixed pain was introduced referring to some low back pain conditions [34].

The prevalence of cancer-related neuropathic or mixed pain (72.1 or 65.5%, based upon the definition employed) was considerably higher than in a recent systematic review (39.1%) [8] and a pan-European survey (32.6%) [35]. This discrepancy probably relates to a biased selection of patients with more advanced disease owing to the use of a convenience sampling procedure. In fact, many patients had advanced or metastatic disease.

This study has a number of limitations. First, its observational, cross-sectional nature precludes evaluating causal relationships. Second, this research is essentially descriptive. Significant results could be affected by multiplicity issues. Nevertheless, the results are valid for inducing hypotheses (such as the presumed higher risk of untoward outcomes in mixed pain patients than in pure neuropathic pain patients). Third, we created an ad hoc pain risk score that cannot be used in cancer pain classification systems, but it has served to pinpoint some syndromes that may pose special difficulties. Fourth, selection biases are probable, as explained. We cannot provide reliable estimates of mixed pain prevalence, and our results may only be applicable to patients with advanced disease. The low accrual per site (eight patients on average) is consistent with the presence of selection biases but it might have in turn enhanced geographical representation. Fifth, opioid doses were not assessed for administrative reasons. Opioid doses are usually higher among cancer patients with neuropathic pain [4].

In conclusion, the presence of a mixed pain pathophysiology may partially explain the complexity of some cancer pain syndromes, making them hard to control. Some syndromes can have an unsuspected mixed pathophysiology and pose particular diagnostic and therapeutic difficulties, in particular tumor-related bone pain (including the involvement of the base of the skull), chemotherapy-induced peripheral neuropathies, malignant chronic hepatic distension/splenomegaly, malignant plexopathies, paraneoplastic pain syndromes, and malignant chronic neuralgias or injury of cranial nerves.

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Author contributions Santiago Ponce developed the protocol, performed clinical evaluations of patients, and supervised the study.

Ana Yuste was the top recruiter and performed clinical evaluations.

Ana Esquivias and Ana Leal developed the protocol and coordinated the study.

Jesús Villoria participated in protocol development, designed and performed the analysis of data, and drafted the manuscript.

All authors participated in the review and extraction of literature, the design of the study, the interpretation of results, and the preparation of the manuscript. All authors had full access to the data and have provided their final approval to the manuscript for publication.

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