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Neuropathic pain: clinical classification and assessment in patients with pain due to cancer

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Abstract

Neuropathic cancer pain (NcP) is associated with worse treatment responses and specific therapy indications, but a standardized clinical diagnosis of NcP is still lacking. This is a prospective observational study on outpatients with cancer, comparing different clinical approaches with NcP evaluation. A three-step assessment of NcP was performed using DN4 (cutoff of 4), palliative care physician Clinical Impression, including etiology and pain syndrome identification, and Retrospective Clinical Classification by a board of specialists with the IASP Neuropathic Pain Special Interest Group criteria. Neuropathic cancer pain classification was specifically referred to pain directly due to cancer. Three hundred fifty patients were assessed, and NcP prevalence was 20% (95% confidence interval [CI] 15.9%-24.6%), 36.9%, (95% CI 31.6%-42.1%), and 28.6% (95% CI 23.8%-33.9%) according to DN4, Clinical Impression, and Retrospective Clinical Classification, respectively. Cohen's kappa concordance coefficient between DN4 and Retrospective Clinical Classification was 0.57 (95% CI 0.47-0.67), indicating moderate concordance. Higher percentages of discordance were found for specific pain syndromes such as pain due to deep soft tissue infiltration and pain associated with tenesmus. Disagreement among clinicians accounted also for different NcP diagnoses and highlighted lack of homogeneous clinical criteria. Rigorous application of etiological and syndrome diagnosis to explain pain cause, associated with standardized diagnostic criteria and assessment of pain characteristics, that is also specific for the cancer pain condition could improve clinical classification of NcP.

Keywords: Neuropathic, Cancer pain, Pain syndromes, DN4

1. Introduction

Pain due to advanced cancer is still a significant clinical problem, with up to 25% of patients experiencing insufficient analgesia.[1,46] In particular, neuropathic cancer pain (NcP), which accounts for at least 20% of pain caused by cancer,[36] has been associated with greater analgesic requirements, poorer outcomes, and greater disability.[9,11,17,19,39] Neuropathic cancer pain is not always well defined and can be difficult to identify.[3,4,10,35] These observations emphasize the need for a reliable identification of neuropathic mechanisms in pain due to cancer.

In this article, we refer to NcP as pain directly caused by cancer progression, which is therefore distinguished from neuropathic pain due to cancer treatment. Because cancer infiltration is associated with local inflammation and tissue damage, leading to nociceptive activation,[45] experts often discuss the presence of a mixed nociceptive and neuropathic pain, as pure neuropathic mechanisms can rarely, if ever, be the only pathophysiology underlying pain due to cancer.

The identification of NcP needs to consider, first, the etiology explaining how pain is caused by the cancer lesion or lesions. Usually, this is done using clinical and imaging findings. Long-standing clinical experience has led to the description of cancer pain syndromes and checklists, which recognize the type and number of tissue lesions causing the pain.[14,15,22,26,28] Different pain characteristics proved to have a different distribution across this syndrome classification.[12] This description distinguishes between pain due to cancer lesions of bone, visceral, soft, and nervous tissues,[17,22,30,33] in agreement with the recent *ICD-11* classification system for cancer pain, which is also based on distinguishing the cancer tissue involvement causing pain.[3]

To date, clinical methodologies to define NcP have been quite variable, including any pain caused from a cancer-induced neurological lesion,[17] pain condition in which there is a combination of a neurological lesion with some specific symptoms,[16] the application of screening tools such as the LANSS,[2] DN4 (Douleur Neuropathique 4 questions) questionnaire,[7] painDETECT,[23] or just the clinician unspecified clinical impression.[8,24,29,35] The IASP Special Interest Group on Neuropathic Pain (NeuPSIG) criteria for identifying neuropathic pain[27,31] have been occasionally applied to the assessment of pain due to cancer[38] but not systematically evaluated.[35] Thus, a standardized clinical approach in identifying NcP is still lacking.

The aim of this study was to compare different methods used for the diagnostics of NcP: a prospective clinical evaluation made by the treating physician including pain syndrome identification

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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(Clinical Impression), a retrospective board evaluation based on the NeuPSIG criteria (Retrospective Clinical Classification), and the DN4 questionnaire.

2. Methods

2.1. Study design and patient population

This is a prospective cross-sectional study of patients enrolled as part of an ongoing observational longitudinal trial (MOLO study) aimed at studying the interaction between clinical and genetic factors in the modulation of opioid analgesia and side effects in cancer pain. In this article, we analyze data obtained at baseline visits.

From May 2015 to June 2019, patients attending the Palliative Care and Pain Outpatient Clinic at the National Cancer Institute of Milan were assessed with a standardized clinical evaluation. Patients were eligible if they were older than 18 years, had a diagnosis of solid, locally advanced or metastatic tumor, had a life expectancy of 1 month or longer, were experiencing cancer pain in the last 24 hours with intensity ≥4 on a 0-to-10 numerical rating scale (NRS), and were already receiving or needed to start treatment with opioids of the third step of the WHO ladder (morphine, oxycodone, fentanyl, or buprenorphine). Exclusion criteria were the following: presence of psychiatric disease or pathologies that could influence the patient state of consciousness and cognitive capabilities; ongoing antalgic radiotherapy in the last 2 weeks or planned in the 4 weeks after enrollment; documented presence of moderate to severe renal failure (plasma creatinine >1.5 mg/mL with a creatinine clearance <60 mL/min); and use of drugs that could interfere with opioids.

The study was performed in accordance with the Declaration of Helsinki. The MOLO study was approved by the Institutional Research Ethics Committee (INT 153/13), and all enrolled patients provided written informed consent.

2.2. Identification of neuropathic cancer pain

Assessment was performed in 3 steps as follows (**Fig. 1**):

2.2.1. Patient Reported Outcome Measurements

Average and worst pain intensity in the last 24 hours were assessed using 0-to-10 NRSs from the Italian Brief Pain Inventory–Short Form.[13] The Italian version of the DN4 questionnaire[42] was chosen among other similar screening tools based on the type of verbal descriptors contained, availability, and validation in Italian language and its performance.[7] It includes both interview questions and an objective examination. Scores of 4 or above are considered as indicative of the presence of neuropathic pain.[7] The interview consists of 7 verbal pain descriptors (burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching) and was performed by an independent researcher.

2.2.2. Treating physician

Basic demographic and clinical data were collected by the treating physician, a specialist in palliative care and pain management. The treating physician completed the objective part of the DN4 (3 items assessing for sensory abnormalities: pinprick, tactile hypoesthesia, and pain to light touch)[7] and recorded pain location, presence of breakthrough pain, and pain treatment. Afterwards, the treating physician had to identify one or more pain syndrome that best depicted the pain reported by the patient, based on pain characteristics and physical signs as referred by the patient and evaluated during the objective assessment and diagnostic tests using a codified list[14] composed of 4 main categories: bone pain, visceral pain, pain due to soft tissue damage, and pain due to nervous tissue damage. This list was developed based on clinical experience and was initially accepted and field tested by an international study group of pain specialists by the IASP Task Force on Cancer Pain in the 90s.[11,14] For each of the main categories, specific pain syndrome subcategories could be selected based on the pain present. If more than 1 pain was present, the assessment was focused on the worst pain. Based on disease characteristics, clinical history of pain , careful physical examination of the patient, and available diagnostic tests, the treating physician also had to classify pain pathophysiology as nociceptive, neuropathic, or mixed (neuropathic and nociceptive).This level of NcP diagnosis was performed by the palliative care and pain clinic physician according to their clinical practice, and it corresponds to what is often referred to in the literature as "Clinical Impression."[35] In this article, we use this term operationally, although it may sound a semantic understatement in respect with the ordinary practice of medicine. For Clinical Impression, both mixed NcP and NcP only were classified as NcP present. The physician was blinded to the final DN4 result.

2.2.3. Retrospective board classification

The NeuPSIG criteria were applied in consideration of the fact that they account for a diagnostic clinical algorithm for NP and can integrate the methods described above (DN4 and Clinical Impression), which are not explicitly based on the application of standardized criteria. The Retrospective Clinical Classification of pain pathophysiology based on the NeuPSIG criteria was performed by a specialist board composed of 3 pain and palliative care physicians, different from those involved in the enrollment and prospective pain type classification. They based their evaluation on data obtained from electronic medical records (including clinical description and available diagnostic tests at the time of enrollment) and were blinded to DN4 results and Clinical Impression of the treating physician. The diagnosis of NcP was finally made in agreement with the NeuPSIG criteria,[21,27] which include the following:

1. History of relevant neurological lesion or disease,
2. Neuroanatomically plausible pain distribution,

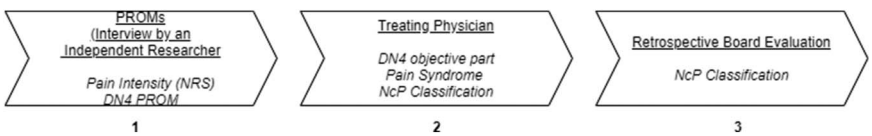

Figure 1. Steps of assessment for the identification of neuropathic cancer pain (NcP). PROMs refer to Patient Reported Outcome Measurements and NRS to numerical rating scale ranging from 0 to 10 for pain intensity measurement.

3. Pain associated with the presence of sensory signs in the same neuroanatomically plausible area,
4. Diagnostic tests confirming a lesion or disease of the somatosensory systems, explaining the pain perceived by the patient.

According to these criteria, neuropathic pain can be determined in the following levels of certainty: possible, probable, and definite.[27] The pain was classified as NcP present by the board if there was a probable or definite presence of neuropathic pain according to the NeuPSIG criteria.

2.3. Statistical analysis

Frequencies and percentages were used to describe categorical variables, whereas means and SDs were used for continuous ones. Point and interval estimates (95% confidence intervals [CIs]) for the prevalence of NcP according to different methods of assessment were calculated. Cohen's kappa was used to estimate the agreement between 2 classification systems.[18] All data analysis was performed using STATA IC 16.[43]

3. Results

3.1. Patient characteristics

From May 2015 to June 2019, a total of 350 patients were enrolled in the study, 192 women and 158 men with a mean age of 63.4 years. **Table 1** reports demographic and clinical characteristics of the study sample. Approximately 94% of patients had metastatic disease, and the most frequent diagnoses were breast (18.9%) and lung cancer (15.4%).

Pain characteristics are reported in **Table 2**; mean values for average and worst pain intensities in the last 24 hours were, respectively, 5.4 and 6.9 (0-10 NRS). The average of pain duration for the group was 12 months, IQ range = 9. The majority (86%) of enrolled patients were already receiving WHO step III opioids, and around 87% of them were also receiving adjuvant drugs for analgesic purposes, mostly steroids (43.7%), bisphosphonates (28.9%), anticonvulsants (28.6%), and NSAIDs (13.4%). The painful syndromes present are listed in **Table 3**. Approximately 53% of the patients had a bone pain component, with pain in the vertebrae and sacrum (32.6%) and pelvic pain (12.9%) being the most common syndromes. Thirty-three percent of patients had visceral pain, and abdominal pain without occlusion was the most common visceral syndrome present (21.2%). Around 25% had pain due to soft tissue damage, and for this group of syndromes, the most common ones were chest or abdominal muscle and fascias infiltration (7.4%) and pleural infiltration (5.7%). Twenty percent of patients had pain due to nervous tissue damage, and peripheral nerve damage due to soft tissue or bony tumor in the limbs (6.3%) was the most frequent pain syndrome present.

The presence of NcP according to the DN4 questionnaire, Clinical Impression, and Retrospective Clinical Classification was, respectively, 20%, 36.9%, and 28.6%. Of the 93 patients (28.6%) evaluated to have NcP by the Retrospective Clinical Classification, 46 patients were classified as having "definite" and 47 "probable" NcP.

3.2. Comparison of Clinical Impression and Retrospective Clinical Classification

Neuropathic cancer pain prevalence according to Clinical Impression and Retrospective Clinical Classification was, respectively, 36.9% (95% CI 31.6%-42.1%) and 28.6%, (95% CI 23.8%-33.9%). **Figure 2** reports a combination of these 2 assessments. The classification of the type of pain was confirmed in 286 patients, 201 (57.4%) without NcP and 85 (24.3%) with NcP. Overall, 39 patients were retrospectively reclassified by the specialist board. Eight (2.3%) were reclassified from NcP absent to NcP present. All of them had a DN4 total score below 4, and 6 had a pain syndrome related to pararectal/perineal soft tissue recurrences/infiltrations resulting clinically in pain associated with tenesmus. Thirty-one patients (8.9%) were reclassified from NcP present to NcP absent. Only 3 of them had a DN4 total score ≥4. Two were reclassified as NcP absent despite positive DN4 because the board evaluated that there was no history of evident neurological somatosensory lesion (NeuPSIG criterion 1) and pain distribution was not considered as neuroanatomically consistent (NeuPSIG criterion 2). The third DN4-positive patient had lumbar bone pain associated with sensory abnormalities in the lower limbs due to chemotherapy-induced peripheral neuropathy. Two further patients with a DN4 below threshold were reclassified because the presence of NP reported by the treating physician was related to chemotherapy-induced peripheral neuropathy. For the other 26 remaining patients with DN4 <4 and with NcP according to Clinical Impression, the pain type was reclassified due to the lack of clear NP characteristics and sensory

Table 1

Demographic and clinical characteristics of patients (n = 350).

Characteristic	No. (%)
Age, mean (±SD)	63.4 (±12.7)
Sex	
Female	192 (54.9)
Male	158 (45.1)
Diagnosis	
Breast	66 (18.9)
Lung/bronchial	54 (15.4)
Gynecological	34 (9.7)
Colon/rectum	31 (8.8)
Pancreatic	29 (8.3)
Prostate	27 (7.7)
Urinary system	22 (6.3)
Stomach/esophageal	17 (4.9)
Liver/biliary tract	15 (4.3)
Head/neck	14 (3.7)
Other/unknown site	43 (12.0)
Presence of metastasis	
Yes	328 (93.7)
No	22 (6.3)
Metastasis location*	
Bone	195 (55.7)
Lymph nodes	162 (46.3)
Liver	115 (32.8)
Lung	110 (31.4)
Abdominal	20 (5.7)
Cerebral	15 (4.3)
Other	125 (35.7)
Antineoplastic therapy	
Yes	238 (68.0)
No	112 (32.0)
KPS	
20-50	42 (12.0)
60-80	274 (78.3)
90-100	34 (9.7)

* A patient can have more than 1 site of metastasis; therefore, the sum is >100%.

Table 2

Pain characteristics of patients (n = 350).

Characteristic	No (%)
Average intensity in the last 24 hours, mean (±SD)	5.4 (±1.4)
Worst intensity in the last 24 hours, mean (±SD)	6.9 (±1.8)
Average of pain duration in months (IQ range)	12 (9)
Breakthrough pain	
Yes	214 (61.1)
No	136 (38.9)
Pain location*	
Cervical, thoracic, or lumbar spine	140 (40.0)
Abdomen	105 (30.0)
Lower limbs	64 (18.3)
Chest	53 (15.1)
Upper limbs	43 (12.3)
Face and neck	12 (3.4)
Head	6 (1.7)
Other	96 (27.4)
Opioids	
III step	
Fentanyl TD	149 (42.6)
Oxycodone	131 (37.4)
Morphine	8 (2.3)
Buprenorphine TD μg/h	4 (1.1)
Hydromorphone	2 (0.6)
More than 1	7 (2)
II step	
Codeine	20 (5.7)
Tramadol	9 (269)
Tapentadol	9 (2.6)
NO opioids	11 (3.1)
Adjuvant therapy*	
Nonsteroidal anti-inflammatory drugs	47 (13.4)
Steroids	153 (43.7)
Anticonvulsants	100 (28.6)
Antidepressants	23 (6.6)
Bisphosphonates	101 (28.9)
Other	101 (28.9)
NO adjuvants	47 (13.4)

* The sum can be more than 100%.

Table 3

Pain syndromes (n = 350).

Pain syndrome	No (%)
Bone pain*	186 (53.1)
Vertebrae and sacrum	114 (32.6)
Pelvic	45 (12.9)
Diffuse bone pain by multiple metastases	35 (10.0)
Long bones	28 (8.0)
Chest wall pain by costal lesions	15 (4.3)
Infiltration of joints	2 (0.6)
Pathological fractures of vertebrae	2 (0.6)
Cefalea from mandibular or maxillary fracture	1 (0.3)
Diffuse bone pain by bone marrow infiltration/ expansion	1 (0.3)
Pathological fractures of long bones	1 (0.3)
Pathological fractures of other	1 (0.3)
Visceral pain*	115 (32.9)
Abdominal pain without occlusion	74 (21.1)
Rostral retroperitoneal syndrome	24 (6.9)
Perineal pain from rectal and perirectal tissue infiltration	13 (3.7)
Distention of the hepatic capsule	9 (2.6)
Suprapubic pain from bladder infiltration	4 (1.1)
Uterus infiltration	4 (1.1)
Anal canal infiltration	3 (0.9)
Biliary obstruction	3 (0.9)
Esophageal	2 (0.6)
Shoulder pain from infiltration of the diaphragm	2 (0.6)
Upper left quadrant from splenomegaly	1 (0.3)
Pain from soft tissue damage*	87 (24.9)
Chest and abdomen muscle and fascias infiltration	26 (7.4)
Pleural infiltration	20 (5.7)
Retroperitoneal infiltration or distension	14 (4.0)
Head–neck muscle and fascias infiltration	14 (4.0)
Limb muscle and fascias infiltration	13 (3.7)
Skin and subcutaneous infiltration	6 (1.7)
Presacral recurrence	4 (1.1)
Perineal recurrence	3 (0.9)
Pain from nervous tissue damage*	71 (20.3)
Peripheral nerve syndrome due to soft tissues or bony tumor in the limbs	22 (6.3)
Lumbosacral plexopathy	13 (3.7)
Peripheral nerve syndrome due to chest wall or abdominal mass	11 (3.1)
Radiculopathy or cauda equina due to vertebral lesion	11 (3.1)
Brachial plexopathy	8 (2.3)
Sacral plexopathy	5 (1.4)
Cervical plexopathy	2 (0.6)
Cranial nerve neuropathy from bone/soft tissue tumor or lesion	2 (0.6)
Peripheral nerve lesion from paraspinal masses	1 (0.3)

* Calculated by the presence of at least one of the syndrome group subtypes.

abnormalities (NeuPSIG criterion 3). Eighteen of 26 of these patients had bone pain, mainly due to vertebral, long bone, or pelvic metastases usually radiating to the limbs but without objective findings of neurological lesion.

For 25 of the 350 enrolled patients (7.1%), the Retrospective Clinical Classification was not possible due to the incomplete information available in the clinical records. Therefore, in the group of the 325 patients, for whom Retrospective Clinical Classification was possible, the overall agreement on the type of pain with the Clinical Impression was 88% (286 of 325 patients).

3.3. Comparison between Retrospective Clinical Classification and DN4 results

This analysis was performed on the 325 patients for whom the Retrospective Clinical Classification was available. The estimated NcP prevalence based on the Retrospective Clinical Classification was 28.6%, 95% CI (23.8%-33.9%), whereas it was 20%, 95% CI (15.9%-24.6%) based on the DN4 questionnaire results. Cohen's kappa indicated a moderate concordance (kappa = 0.57, 95% CI [0.47-0.67]). **Figure 3** shows an overall agreement between the 2 methods in 84.3% of cases (15.4% on the presence of NcP and 68.9% on absence). In 43 patients (13.2%), the Retrospective Clinical Classification was positive for NcP, but the DN4 was below the threshold of 4; the opposite happened in only 8 patients (2.5%). To examine potential reasons for disagreement in the former 43 patients, we calculated the percentage of discordance (DN4 below threshold vs clinical evaluation positive) by specific pain syndromes (**Fig. 4**). Higher discordance emerged in patients affected by pain due to damage

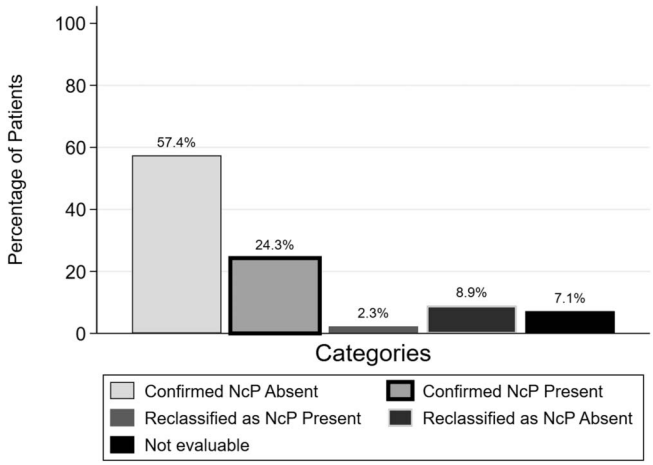

Figure 2. Classification of cases based on the comparison of pain type assessment and the presence of neuropathic cancer pain (NcP) between the Clinical Impression and Retrospective Clinical Classification (N = 350).

of soft or nervous tissue, especially for syndromes such as perineal pain due to rectal and perirectal tissue infiltration or infiltration of muscles and fascias of the limbs. In fact, 14 of these 43 patients had a syndrome of perineal pain due to rectal and perirectal tissue infiltration, associated with tenesmus. The DN4 score was 0 for 6 of these 14 patients and 2 for the remaining 8, of whom, only 1 had significant sensory findings in the physical examination. Of the remaining 29 patients, 9, 9, 6, and 5 patients had a DN4 of 3, 2, 1, and 0, respectively, and the pain syndromes included a combination of a bone and nervous tissue damage (11 patients), soft tissue and nervous tissue damage (7 patients), only soft tissue damage (5 pts), bone and soft tissue damage (2 patients), bone, soft tissue, and nervous tissue damage (1 patient), only bone pain (1 patient), and only nervous tissue damage (1 patient). In all of them, the board of experts identified signs of neurological lesion associated with pain distribution.

3.4. Description of pain syndromes by Retrospective Clinical Classification according to the IASP Special Interest Group on Neuropathic Pain criteria

Table 4 reports the distribution of pain syndromes by the presence/absence of NcP according to the Retrospective Clinical Classification in the group of 325 evaluated patients. Pain due to only bone or only visceral lesions were more frequently encountered in patients without NcP, with a prevalence of 45% and 32%, respectively, over 232 cases compared with 5% and 13% over 93 cases of NcP. Instead, for patients with NcP, the combination of bone and nervous tissue damage (39%) and that of soft tissue and nervous tissue damage (16%) accounted for the most frequent syndromes. For patients without NcP, there was only 1 patient with a combination of bone and nervous tissue damage, whereas there were no cases with both soft and nervous tissue damage. Among patients with NcP, 2 (2%) had evidence of only nervous tissue damage.

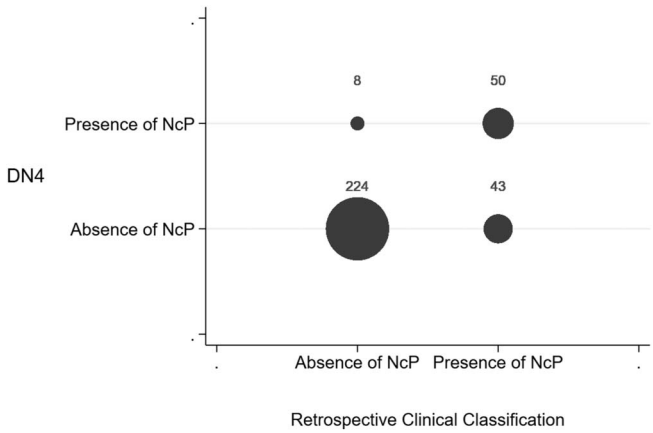

Figure 3. Pattern of concordance–discordance regarding neuropathic cancer pain (NcP) assessment between DN4 and Retrospective Clinical Classification (N = 325).

4. Discussion

The classification of cancer pain dates back to the pivotal reports by Foley and colleagues in 1979[22] describing the complexity of pain syndromes caused by cancer direct or metastatic invasion of potentially any body tissue. The diagnosis of the cause and mechanism of cancer pain impacts both analgesics prescription and antineoplastic palliative interventions.[22,25] An accurate clinical description of the pain-causing lesion and pain clinical characteristics is also necessary for describing homogenous groups when addressing analgesic or palliative therapeutic interventions in clinical trials and in the clinic.[5,16]

Our study shows an acceptable level of agreement between different methods (88.0% between Clinical Impression and Retrospective Clinical Classification; 84.3% between the latter and the DN4), but most of this agreement is concentrated on the absence of NcP, as could be expected due to the limited prevalence. In addition, the descriptive analysis of the cases of discordance shows higher amount of disagreement for specific pain syndromes.

This points to a substantial variability among physicians' identification of NcP, especially for some specific pain syndromes such as those related to pararectal–pelvic soft tissue infiltrations resulting in pain associated with tenesmus. In some cases, this was considered as mixed pain and in others nociceptive, depending on Clinical Impression of the treating physician. In the Retrospective Clinical Classification, perineal and pelvic pain associated with tenesmus and due to soft tissue local relapse was diagnosed as mixed nociceptive and neuropathic pain. A recent systematic review has described the lack of homogeneous understanding of the pathophysiology of tenesmus.[37] Differences between the Clinical Impression and the Retrospective Clinical Classification were also seen in the presence of bone vertebral lesions with pain radiating into the limbs, often defined neuropathic after Clinical Impression (31 cases) but considered to not fulfill the NeuPSIG criteria for probable or definite NP in the Retrospective Clinical Classification. In very few cases, the treating physicians did not clearly separate pain due to cancer from pain due to treatment. The fact that not every pain in an oncological patient is caused by the tumor itself is very important because pain due to antineoplastic treatment or other comorbidities can often be found.[26]

Our study also revealed a moderate concordance between the Retrospective Clinical Classification and the DN4 questionnaire (Cohen's kappa = 0.57). The prevalence of NcP obtained from the Retrospective Clinical Classification (28.6%) was higher than the one obtained by the DN4 (20%), but resulted similar to that reported in the available literature.[4,41] The evidence available about the agreement between NcP evaluation in clinical practice and DN4 questionnaire in patients with cancer is limited. Results from a multicenter study of 8615

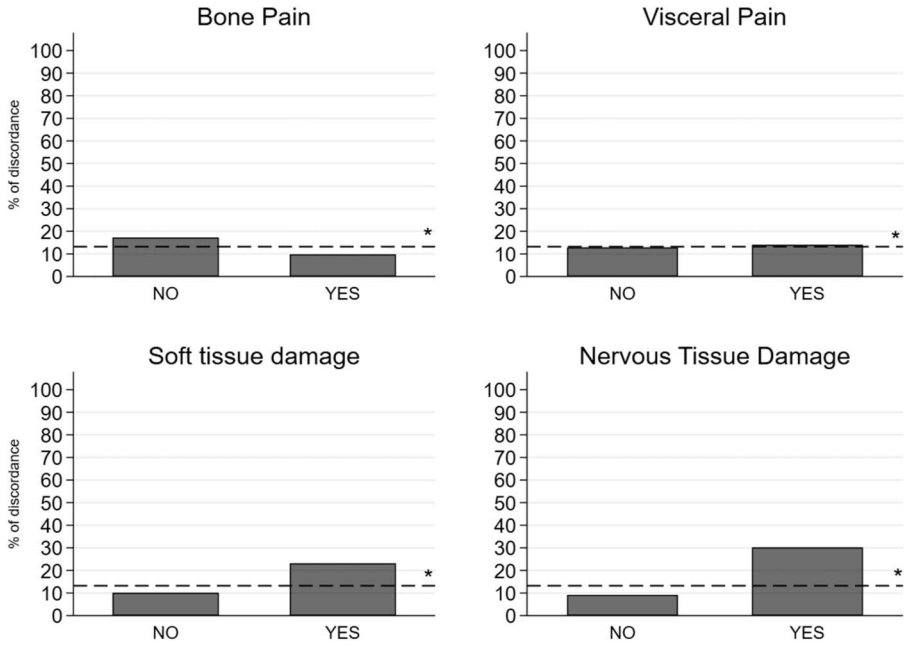

Figure 4. Percentage of discordance (DN4 below threshold vs Retrospective Clinical Classification positive) for the specific pain syndrome categories (N = 325). *The black dotted line indicates the % (13.2%) of the specific pattern of discordance (DN4 below threshold vs Retrospective Clinical Classification positive) in the overall sample.

patients with cancer in Spain[24] revealed that only about half of cases diagnosed as neuropathic by clinicians were identified also by the DN4. However, criteria used by the oncologists to diagnose NcP were not described, and no etiological classification of pain was provided. A Greek study showed an agreement of 79% between DN4 and Clinical Impression by pain specialist, but also here the criteria used by the specialist were not specified.[44] In another study,[40] NcP was diagnosed also by pain specialists, without explicit use of clinical criteria, but a distinction between pain due to cancer or treatment was provided. A neuropathic pain component was identified by physicians in 66% of patients (246 over 371), and only 120 (32.3%) of them had a DN4 ≥4. In a study by Bouhassira et al.,[8] the DN4 result was consistent with the investigator's clinical judgment in 88.1% of cases. A differentiation of pain etiology was also provided, with about half of the cases suffering from pain due to cancer and half from pain due to treatment, but this difference was not considered in accounting for the neuropathic pain diagnoses. In only 1 study,[38] the IASP definition of neuropathic pain was applied by pain specialists and was compared with the DN4 results showing a good agreement, although, also in this case, no distinction between pain due to

Table 4

Affected tissues and presence of NcP according to the Retrospective Clinical Classification (n = 325).

Affected tissue	Absence of NcP		Presence of NcP		Total
	N	% (95% CI*)	N	% (95% CI†)	N (%)
Only bone	105	45 (39-52)	5	5 (2-12)	110 (33.8)
Only visceral	76	33 (27-39)	12	13 (7-21)	88 (27)
Only soft tissue	29	12.5 (9-17)	7	8 (3-15)	36 (11.1)
Only nervous tissue	0	0 (—)	2	2 (0-7.5)	2 (0.6)
Bone and visceral	7	3 (1-6)	1	1 (0-6)	8 (2.5)
Bone and soft tissue	8	3.5 (2-7)	3	3 (1-9)	11 (3.4)
Bone and nervous tissue	1	0.5 (0-2)	36	39 (29-49)	37 (11.3)
Soft and nervous tissue	0	0 (—)	15	16 (9-25)	15 (4.6)
Visceral and soft tissue	5	2 (1-5)	3	3 (1-9)	8 (2.4)
Visceral and nervous tissue	0	0 (—)	2	2 (0-7.5)	2 (0.6)
Bone, visceral, and soft tissue	1	0.5 (0-2)	0	0 (—)	1 (0.3)
Bone, soft, and nervous tissue	0	0 (—)	7	8 (3-15)	7 (2.2)
Total	232	100%	93	100%	325 (100%)

* Percentage estimated over 232 patients without NcP.
† Percentage estimated over 93 patients with NcP.
NcP, neuropathic cancer pain.

cancer or treatment was provided. We compared our results with other authors' work in terms of agreement and decided not to calculate specificity and sensitivity values as we find it not legitimate to consider the classification based on "clinical impression" or NeuPSIG criteria as the "gold standard." When considering screening tools for NP, it should be, however, kept in mind that the majority of these tools, including the DN4, have been developed and validated[7] in pain populations different from patients with cancer pain, explaining probably part of the discordance.

The descriptive analysis indicates that the presence of specific pain syndromes was associated also with higher discordance between the Retrospective Clinical Classification and DN4. This was true for syndromes of pain from soft tissue damage, especially for pain syndromes due to infiltration of muscles and fasciae in the limbs or perineal pain due to rectal and perirectal tissue infiltration. For the latter, the presence of rectal tenesmus is characteristic, and, as seen above, its classification differed also among physicians. The tendency of cancer to infiltrate peripheral neural structures, which provide somatic sensory afferent innervation but also deep soft tissues such as muscles, fasciae, and synovial tissues, makes it difficult to identify symptoms of hyperalgesia, allodynia, and neuronal function loss. These symptoms are typically described for NP associated with peripheral nervous or central somatosensory lesions usually involved in the pain syndromes, which guided the construction of questionnaires such as the DN4. This is the case of tenesmus. If tenesmus should be classified as a neuropathic condition, the DN4 or other questionnaires of the same kind are inadequate to screen it. Less discordance between the clinical evaluation and DN4 was found for abdominal visceral pain syndrome. A study conducted in 7 Canadian academic pain centers has also revealed that questionnaires such as the DN4 perform differently according to the specific pain syndrome present.[47]

This study offers a broad representation of cancer pain etiologies and classification and uses of 3 different approaches for NcP diagnosis, referring specifically to pain directly caused by the tumor. Although we refrain from defining any of the above-described assessments as "a golden standard," the use of clinical criteria seems necessary to support a homogeneous identification of NcP, and the available NeuPSIG criteria can be a reasonable choice. Yet, their application to the cancer pain population should follow some adaptation to the characteristics of this population.[6,10,36] In 2014, the EAPC/IASP algorithm for diagnostic criteria of NcP was proposed[10]; however, it still needs validation. The recent proposal of the *ICD-11* classification[3] allows us to describe bone-related cancer pain, visceral cancer pain, and pain due to neurological lesions. Unfortunately, it does not allow us to classify soft tissue cancer lesions, which, in our study, accounted for more than 25% of pain syndromes. It is clear that depending on the tissues involved and on peripheral and central pain pathway changes involved, inflammatory, nociceptive, and neuropathic mechanisms can be at stake at the same time in patients with cancer, and therefore, NcP is rarely found as the consequence only of a neurological lesion.[34] This was evident also in our study in which only in 2 of the patients diagnosed with NcP, the underlying cause was the damage of the nervous tissue alone. It is also possible that specific cancer pain pathophysiologies may overrule the traditional distinction between nociceptive and neuropathic pain as associated with chronic nonmalignant pain conditions, but more research is needed to address this hypothesis and its eventual clinical impact.[20]

Considering our study limitations, the 350 patients included in this article were enrolled as part of a prospective longitudinal study, and they were accrued based on a significant number of inclusion and exclusion criteria. Only patients with pain ≥4 in need or already receiving opioids of the third step of the WHO analgesics ladder were enrolled; therefore, some of the patients were already known to the physicians and were also receiving adjuvant therapy for the neuropathic component. It is possible that somehow this could have affected not only the results obtained by the DN4 but also the evaluation of NcP made by the treating physician. On the other hand, our study is a single-center study, and this could have an impact on the generalizability; therefore, we believe that these results should be tested in multicenter trials. The retrospective application of the NeuPSIG grading system is another limitation of the study, as the experts could not personally examine the patients, and therefore, our results need to be tested in a prospective trial.

5. Conclusions

The high heterogeneity of cancer pain makes a standardized approach for the assessment of NcP essential to improve the results of treatment and future clinical and preclinical studies. This was considered urgently needed in 2011 by an international initiative and expert consensus meeting held in Milan, and it seems to us that little progresses were made so far.[32]

From the results obtained in this study, we propose a standardized checklist approach to recognize cancer pain etiology and syndromes. This first etiological information obtained by syndrome identification, combined to Patient Reported Outcome Measurements, as those included in the DN4, and clinical criteria similar to the ones suggested by the NeuPSIG, could translate into better identification of the type of pain present.[10] Prospective evaluation of this methodology in future studies should address its clinical usefulness and impact and integrate pain characteristics, which may fail available diagnostic criteria.

Conflict of interest statement

A. Caraceni reports personal fees from Kyowa Kirin, Grunenthal GmbH, Pfizer, Almirall, Helsinn Healthcare, Molteni & C Soc Esercizio Spa, Shionogi, Italfarmaco, Sandoz International GmbH, and Institute de Recherche "Pierre Fabre" and grants from Molteni & C Soc Esercizio Spa, ProStrakan, Grunenthal GmbH, Amgen, and Ipsen, outside the submitted work. S. Kaasa reports personal fees from Fresenius Kabi, personal fees and grants from Nutricia, and other from Eir Solution, outside the submitted work. E. Zecca reports grants from Amgen srl, outside the submitted work. M. Shkodra reports grants from EU Research Framework Programme H2020/Marie Skłodowska-Curie Actions, during the conduct of the study, and other from Angelini, outside the submitted work. The remaining authors have no conflicts of interest to declare.

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