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An international survey of cancer pain characteristics and syndromes

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Abstract

The optimal assessment of cancer pain includes a detailed description of pain characteristics and classification by both syndrome and likely mechanisms. In the clinical setting, the interpretation of this information is aided by knowledge of the available clinical experiences on these aspects of the pain. Unfortunately, existing data are limited. There have been few large surveys of cancer pain characteristics and syndromes, and comparative data from patients in different parts of the world are entirely lacking. To better define the characteristics of cancer pain syndromes the Task Force on Cancer Pain of the International Association for the Study of Pain (IASP) conducted a prospective, cross-sectional, international, multicenter survey of pain specialists and their patients. From a total of 100 clinicians who described themselves as cancer pain practitioners in the IASP membership directory, 51 agreed to participate in the survey and a total of 58 provided data. These clinicians resided in 24 countries and evaluated a total of 1095 patients with severe cancer pain mostly requiring opioid medication, using a combination of patient-rated and observer-rated measures. The patient-rated scales comprised a pain intensity measure chosen from the brief pain inventory. The observer-rated information included demographic and tumor-related data, and responses on checklists of pain syndromes and pathophysiologies. Patients were heterogeneous in terms of demographics and tumor-related information. More than 76% had a Karnofsky performance status score ≤ 70. Almost one-quarter of the patients experienced two or more pains. A large majority of the patients (92.5%) had one or more pains caused directly by the cancer; 20.8% of patients had one or more pains caused by cancer therapies. The average (SD) duration of pain was 5.9 (10.5) months. Approximately two-thirds of patients (66.7%) reported that the worst pain intensity during the day prior to the survey was $\geqq 7$ on a 10-point numeric scale. The factors that were univariately associated with higher pain intensity included the presence of breakthrough pain, somatic pain or neuropathic pain, age younger than 60 years, and lower performance status score. A multivariate model suggested that the presence of breakthrough pain, somatic pain, and lower performance status were the most important predictors of intense pain. Pains that were inferred by the treating clinician to be nociceptive and due to somatic injury occurred in 71.6% of the patients. Pains labeled nociceptive visceral were noted in 34.7% and pains inferred to have neuropathic mechanisms occurred in 39.7%. In a broad classification, the major pain syndromes comprised bone or joint lesions (41.7% of patients), visceral lesions (28.1%), soft tissue infiltration (28.3%), and peripheral nerve injuries (27.8%). Twenty-two types of pain syndromes were most prevalent. Large differences in the diagnosis of breakthrough pain by clinicians of different countries suggest that this phenomenon is either defined or recognized differently across countries. These data confirm, in segment of the cancer population experiencing severe pain, in different parts of the world, that cancer pain characteristics, syndromes and pathophysiologies are very heterogeneous. Predictors of worsening pain can be identified. The data provide a useful context for the interpretation of pain-related information acquired in both clinical and research settings. They suggest the need for future studies and the potential usefulness of a written checklist for cancer pain syndromes and pathophysiologies.

Keywords: Cancer pain syndromes; Cancer pain classification

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1. Introduction

Among many other objectives, the comprehensive assessment of the patient with cancer pain seeks to define the characteristics of the pain, clarify the relationship between the pain and the neoplasm, and label both the pain syndrome and the likely mechanism or mechanisms that may be sustaining the pain (Cherny and Portenoy, 1994). This information can have important clinical implications in recognizing disease progression. It may guide the selection of further laboratory or radiographic studies, or suggest specific therapeutic interventions (Gonzales et al., 1991). Given the evidence that cancer pain is usually caused by the neoplasm itself and is often the first indicator of tumor recurrence or progression, the importance of a comprehensive pain assessment for optimal management of both the symptom and the disease is clear.

Cancer pain syndromes are identified by a constellation of pain characteristics, physical signs, and data from laboratory, electrodiagnostic and radiographic tests (Gonzales et al., 1991). Numerous syndromes have been described, many efforts have been made to create and update a syndrome classification (Foley, 1979; Greenberg et al., 1981; Kori et al., 1981; Arner and Arner, 1985; Jaeckle et al., 1985; Bruera et al., 1989; Vecht et al., 1989; Vecht, 1990; Ventafridda and Caraceni, 1991; Portenoy, 1992; Portenoy et al., 1992, 1994; Vecht et al., 1992; Cheng et al., 1993; Cherny and Portenoy, 1994; Caraceni, 1996; Caraceni and Portenoy, 1996) These efforts consistently demonstrate that cancer pain syndromes are complex and can be related to a variety of etiologic factors and pathophysiological mechanisms.

Although the pathophysiologies underlying a pain syndrome cannot be precisely determined, it is now conventional practice to infer the predominating type of mechanism or mechanisms on the basis of clinical information (Arner and Arner, 1985; Ashby et al., 1992; Portenoy, 1992). Pain is labeled nociceptive if the sustaining mechanisms are believed to be related to ongoing tissue injury. Nociceptive pain is usually subdivided into somatic and visceral types, based on the nature of the tissue injury. Pains are usually labeled neuropathic if there is evidence that the pain is associated with injury to neural tissues and is sustained by aberrant somatosensory processing in the periphery or in the central nervous system. The generic term, psychogenic pain, is often used to label pains that are believed to be predominantly determined by psychological factors. Although variations of these terms have been used (e.g. superficial somatic pain versus deep somatic pain, and neurogenic pain versus neuropathic pain), and some controversies exist (e.g. regarding the existence of a nociceptive nerve pain) (Asbury and Fields, 1984), there is general acceptance of the view that classification by inferred pathophysiology can have clinical utility.

As cancer pain assessment becomes more sophisticated, surveys that describe specific pain-related phenomena are yielding information that has direct relevance to patient care. For example, the evidence that the presence of breakthrough pain and a neuropathic pathophysiology both predict a lesser responsiveness to opioid therapy (Kaiko et al., 1983; Arner and Arner, 1985; Bruera et al., 1989, 1995; Banning et al., 1991; Brose and Cousins, 1991; Mercadante et al., 1992, 1994; Cherny et al., 1994; Vigano et al., 1996) may suggest the need to improve clinical monitoring and perhaps alter the treatment of patients with these characteristics.

Additional information about pain characteristics, syndromes, and pathophysiologies could potentially provide a useful background for the interpretation of other pain-related information. Unfortunately, such data are quite limited. There have been few large surveys of cancer pain characteristics and syndromes, and there are no comparative data from patients in different parts of the world. Surveys have not been done to confirm that physicians in different countries apply a common language to describe aspects of the pain.

The Task Force on Cancer Pain of the International Association for the Study of Pain (IASP) conducted a survey of pain specialists and their patients in numerous IASP member countries around the world. Within the limits of patients selection posed by our methods, the results describe the phenomenology of cancer pain in a large multilingual and multicultural population, and concurrently suggest the usefulness of a checklist for cancer pain syndromes and pathophysiologies that could potentially be used for clinical or research purposes by pain specialists in different part of the world.

2. Methods

2.1. Procedures

This prospective, cross-sectional, multicenter survey was initiated through contacts with 100 physicians who were members of IASP and identified cancer pain as their main interest in the IASP membership directory. These clinicians were contacted by mail and queried about their interest in participating. Some of those who responded affirmatively ($N = 51$) subsequently identified additional co-investigators at the same site. A total of 58 clinicians from 24 countries confirmed their desire to participate by completing a questionnaire that acquired information about personal characteristics and practice patterns. After returning the questionnaire, each investigator received a packet of patient questionnaires.

Investigators were told to evaluate consecutive patients older than 16 years who had active cancer and were experiencing a chronic pain severe enough to require opioid medication. Patients were excluded if the investigator believed that they had significantly compromised cognitive function or were imminently dying. Investigators were asked to

accrue 20–50 patients. Patient accrual began in January 1995 and was terminated in June 1996, by which time 1095 patients had been accrued.

2.2. Instruments

2.2.1. Investigator questionnaire

The investigator questionnaire recorded age, gender, years since completion of medical school, medical specialty, practice site (e.g. community hospital, university hospital, or hospice), years treating cancer patients for at least 20% of practice time, and the time dedicated to care of cancer patients during the month preceding questionnaire completion. The modalities available for the treatment of cancer pain, including anti cancer treatments (chemotherapy, radiation and surgery) and opioids (oral and parenteral) for in-hospital and home care use, were specifically questioned.

2.2.2. Pain questionnaire

The pain questionnaire recorded information about the patient's demography, disease, and pain. All the items were completed by the investigator except for pain intensity data, which was acquired directly from patients.

2.2.2.1. Cancer diagnosis and extent of disease. The neoplasm was indicated on a checklist of 21 common cancers. Extent of disease was labeled as none, local or loco regional, or metastatic.

2.2.2.2. Performance status. Performance status was evaluated using the observer-rated Karnofsky performance status (KPF) score. This score is a valid indicator of physical functioning (Yates et al., 1980).

2.2.2.3. Pain characteristics. The investigators recorded the number of different types of pain, if more than one was described by the patient. If more than one type was noted, investigators were told to focus on the worst pain, i.e. the pain with the most important clinical implications, for the subsequent questions. A separate question asked the investigator to note the presence of breakthrough pain, which was defined as an episode of 'pain flare' of any duration superimposed on a baseline pain.

The investigators were asked to label the pain (the worst pain if more than one type) as caused by the tumor, tumor treatment, or factors unrelated to tumor or treatment. They also recorded the duration of this pain, as reported by the patient, and noted the type of diagnostic testing (e.g. plain radiographs, computerized tomography, magnetic resonance imaging, or others) that was performed to elucidate the nature of this pain. Pain treatments were described, and there were specific queries about the administration of analgesic drugs.

All patients completed language-appropriate pain intensity scales. The scales were numeric, and were either included within the Brief Pain Inventory (BPI) (Daut and Cleeland, 1982; Daut et al., 1983; Cleeland et al., 1994; Serlin et al., 1995) or were adapted from this instrument. The 0–10 numeric scales included in this instrument are anchored by 'no pain' and 'pain as bad as you can imagine'. Four separate scales assessed pain 'right now' pain 'at its worst' during the past day, pain 'at its least' during the past day, and pain 'on average'during the past day, respectively.

Patients whose native language was English, French, Spanish, Philippino, or Italian were administered the BPI-short form that had been validated in the appropriate language. Patients who spoke other languages had the word anchors for the numeric scales translated by the investigator.

2.2.2.4. Inferred pathophysiology. The investigators were given a checklist for the worst or only pain that included the following descriptors: nociceptive somatic, nociceptive visceral, neuropathic, and psychogenic. Definitions of these terms were not provided. More than one could be checked if, in the judgment of the investigator, this designation most appropriately described the pain.

2.2.2.5. Pain syndrome. A checklist of pain syndromes was elaborated by the authors and revised based on the independent comments of four reviewers (see Acknowledgement). The checklist included 51 tumor-related pain syndromes (34 main diagnoses, with subdiagnoses in some cases) and 18 treatment-related pain syndromes (six main diagnoses, with subdiagnoses in some cases)(see below). Investigators were told to check one, or more than one syndrome that best depicted the worst or only pain reported by the patient. A syndrome that was not in the checklist could be written. To reinforce understanding of the syndrome checklist, a review article (Cherny and Portenoy, 1994) was included with the questionnaire packet.

2.3. Data analysis

The responses to each item in the investigator questionnaire and the pain questionnaire were tabulated and frequency distributions were determined for key variables, such as pain syndromes and pathophysiologies. For the purposes of the analysis, the scores on the numeric pain intensity measure for 'worst pain' were divided into three groups, 0–4, 5–6, and 7–10. This clustering was based on a combined analysis of a large dataset that indicated an association between the extent of pain-related functional decline and these levels of pain (Serlin et al., 1995). These association with functional decline suggest that worst pain levels of 0–4, 5–6, and 7–10 can be likened to mild, moderate, and severe pain, respectively.

For patients with pain caused by the neoplasm ($N = 1007$, 92% of the total sample), the associations between worst pain intensity (categorized as indicated above) and both demographic and clinical characteristics

Table 1
Number of patients accrued by each participating country

Country	*N*	%
Australia	70	6.4
Canada	52	4.7
Chile	12	1.1
Colombia	13	1.2
Denmark	135	12.3
Finland	41	3.7
France	81	7.4
Germany	76	6.9
Greece	30	2.7
Holland	37	3.4
India	89	8.1
Israel	10	0.9
Italy	62	5.7
Mexico	10	0.9
Norway	10	0.9
New Zealand	10	0.9
Panama	25	2.3
Philippines	10	0.9
Portugal	20	1.8
People's Republic of China	30	2.7
Republic of China	42	3.8
Russia	46	4.2
Spain	50	4.6
Thailand	43	3.9
USA	91	8.3
Total	1095	100

were evaluated using univariate and multivariate cumulative logit models (Agresti, 1990). In these analyses, worst pain intensity was used as the dependent variable and only those variables that were significantly associated with pain in a univariate analysis were included in the multivariate analysis. These results are presented in terms of cumulative odds ratios, with 95% confidence intervals (CI). As a proportional odds assumption could not be verified for any of the independent variables, two different cumulative odds ratios were estimated for each analysis, one for the cutoff between mild and moderate pain (worst pain scores 0–4 versus 5–6) and another for the cutoff between moderate and severe (worst pain scores 5–6 versus 7–10). A cumulative odds ratio >1 for a specific characteristic indicates that the odds of experiencing pain greater than or equal to the cutoff is higher for patients with this characteristic than for patients without it. For example, if the analysis using the cutoff between moderate and severe pain demonstrates an odds ratio of 1.5 for breakthrough pain, this value indicates that the odds of experiencing a worst pain level of 7–10 are 1.5 times higher for patients with breakthrough pain than for those without breakthrough pain.

3. Results

3.1. Investigators

Questionnaires were available from the original 51 physicians who agreed to participate in the study. Approximately 64% were anesthesiologists; 16% were internists (10% oncologists), and almost 20% were other disciplines. The mean (SD) number of years in practice was 15.4 ± 7.4. About 80% had been treating cancer pain patients for more than 5 years and 70% dedicated 50% or more than their professional time to cancer pain patients. Their affiliations included university hospitals (73%), community hospitals (23%), and hospices (4%). Resources available for patient care included outpatient clinics (98%), hospital beds (94%), home care (84%), and hospice beds (59%). Table 1 shows the number of patients provided to the survey by each of the 24 countries.

3.2. Patient demographics and disease-related variables

The sample ($N = 1095$) was evenly divided between men and women. The mean age was 58.2 years (SD = 14.6). Cancer diagnoses were diverse and almost 70% of the patients had metastatic disease at the time of the assessment (Table 2). More than three-quarters of the patients required substantial help to function physically (KPS score ≤ 70).

Table 2
Demographics and disease-related variables

Variables	Number	%
Gender		
Male	554	50.6
Female	541	49.4
Missing	0	
Age	Mean = 58.2 (SD = 14.6)	
Missing	38	
Diagnosis		
Lung	197	18.1
Breast	146	13.4
Head and neck	111	10.2
Pancreas, stomach	105	9.6
Esophageal		
Colon-rectum	103	9.5
Uterus	72	6.6
Prostate	65	6.0
Leukemia, lymphoma	43	3.9
Other	247	22.7
Missing	6	
Extent of disease		
None	34	3.1
Local	297	27.3
Metastatic	758	69.6
Missing	6	
Karnofsky performace status		
10–40	267	24.6
50–70	563	51.8
80–100	256	23.6
Missing	9	

Table 3
Pain related variables

	Number	%
Pain cause[a]		
Pain due to tumor	1007	92.5
Pain due to tumor treatment	226	20.8
Pain unrelated to tumor or treatment	25	2.3
Number of pains		
1	788	75.2
2	179	17.1
3	65	6.2
4	12	1.1
>4	4	0.4
Missing	47	
Pain duration – months		
Mean (SD) = 5.9 (10.5)		
Missing	30	
Pain pathophysiology		
Somatic nociceptive only	354	32.3
Somatic and neuropathic	255	23.3
Visceral nociceptive only	166	15.2
Somatic and visceral	118	10.8
Neuropathic only	84	7.7
Somatic, visceral and neuropathic	57	5.2
Visceral and neuropathic	39	3.6
Unknown only	19	1.7
Other with psychogenic	17	1.5
Psychogenic only	3	0.3
Breakthrough pain		
Yes	615	64.8
No	334	25.2
Missing	146	
Worst pain intensity[b]		
0—4	138	12.9
5—6	222	20.6
7—10	721	66.7
Missing	14	
Average pain intensity[c]		
0—4	504	47.2
5—6	352	32.9
7—10	212	19.9
Missing	27	
Least pain intensity[d]		
0—4	872	80.7
5—6	143	13.2
7—10	65	6.1
Missing	15	
Pain right now intensity[e]		
0—4	646	59.9
5—6	219	20.3
7—10	213	19.8
Missing	17	
Pain therapy		
Non-opiods	736	69.4
Opioids	985	90.8
Adjuvants	373	36.2
Others	160	16.1

[a] Each patient may have more than one.
[b] Mean (SD) = 7.2 (2.2).
[c] Mean (SD) = 4.7 (2.1).
[d] Mean (SD) = 2.6 (2.2).
[e] Mean (SD) = 4.0 (2.6).

3.3. Pain-related variables

The pains experienced by these cancer patients were extremely heterogeneous (Table 3). Approximately 25% of the patients had more than one type of pain. More than 20% had one or more pains caused by antineoplastic treatment.

The mean (SD) pain duration at the time of the interview was 5.9 (10.5) months. The physicians ascertained that approximately two-thirds (64.8%) of the patients were experiencing episodes of breakthrough pain in addition to the more continuous background pain. More than two-thirds (66.7%) of the patients reported that their worst pain during the prior day had been severe (between 7 and 10 on the 10 point scale) The mean (SD) 'Worst pain' intensity was 7.2 (2.2.). The mean (SD) 'Average pain' intensity was 4.7 (2.1), 'least pain' intensity was 2.6 (2.2) and 'pain right now' intensity was 4.0 (2.6), respectively. Most patients (91%) were receiving opioid medication when interviewed (Table 3).

3.4. Pain syndromes and inferred pathophysiology

Most physicians used a combination of clinical findings and imaging approaches to establish pain diagnoses. The imaging approaches varied. Plain radiography and computed tomography were used in more than 50% of cases. Bone scintigraphy was used in 35.5%, and ultrasound imaging and magnetic resonance imaging were used in 17 and 13% of cases, respectively. Clinical findings were felt useful in making a diagnosis in 82.2% of cases. The use of clinical findings alone ranged from 0 to 13%, with only three exceptions: Chile (41.6% of 12 patients), India (46.4% of 84 patients) and New Zealand (37.5% of eight patients).

Table 4 reproduces the syndrome checklist that was used to acquire frequency data, along with the prevalence rates for the worst or only syndromes experienced by this population. Investigators were asked to indicate the presence of any syndrome that was not included on the checklist. There were no cancer-related pain syndromes added and only a small number of treatment-related syndromes and syndromes unrelated to cancer or treatment were mentioned. In a broad classification of the cancer-related syndromes, the major grouping comprised bone or joint lesions (41.7% of patients), visceral lesions (28.1%), soft tissue infiltration (28.3%), and peripheral nerve injuries (27.8%).

The types of pathophysiology inferred to be sustaining the pain also varied greatly (Table 3). Pains that were nociceptive and due to somatic injury occurred in 71.6% of the patients. Pains labeled nociceptive visceral were noted in 34.7% and pains inferred to have neuropathic mechanisms occurred in 39.7%.

Twenty-two types of pain syndromes were most prevalent (Table 5). A cross-tabulation of these syndromes and the major tumor types (Table 6) suggests the existence of

Table 4
Cancer pain syndrome checklist

	N	%
A. Pain syndrome related to direct tumor involvement due to lesions of somatic and visceral structures	1053	98.1
A1. Neoplastic damage to bone and joints	447	41.7
Base of the skull syndrome	23	2.1
Headache due to calvarial, maxillary or mandibulary lesion	38	3.5
Vertebral syndromes including sacrum	143	13.0
Pelvis	77	7.1
Long bones	42	3.9
Generalized bone pain		
due to multiple bone metastases	109	10.2
due to bone marrow infiltration – expansion	19	1.8
Chest wall pain from rib lesion	73	6.8
Direct infiltration of a joint	10	0.9
Pathological fracture		
long bone	15	1.4
vertebrae	22	2.0
pelvis	2	0.2
rib	8	0.7
other	7	0.6
A2. Neoplastic damage to viscera	301	28.1
Esophageal mediastinal pain	30	2.8
Shoulder pain from diaphragmatic infiltration	13	1.2
Epigastric pain from pancreas or other upper abdominal cancer rostral retroperitoneal syndrome	85	7.9
Pain from distention of hepatic capsule	67	6.2
Left upper quadrant pain from splenomegaly	4	0.4
Diffuse abdominal pain from abdominal or peritoneal disease		
with obstruction	49	4.6
without obstruction	20	1.9
Suprapubic pain from infiltration of bladder	37	3.4
Perineal pain from infiltration of rectum or perirectal tissue (including vagina)	84	7.8
Obstruction of biliary tract	5	0.5
Obstruction of ureter	13	1.2
A3. Neoplastic damage to soft tissue and miscellaneous syndromes	305	28.3
Damage to oral mucous membranes	31	2.9
Infiltration of skin and subcutaneous tissue	59	5.5
Infiltration of muscle and fascia in the chest or abdominal wall, excluding rib pain due to bony lesion	96	8.9
Infiltration of muscle and fascia in the limbs	16	1.5
Infiltration of muscle and fascia in the head and neck	56	5.2
Retroperitoneal tissue infiltration or distension (does not include rostral retroperitoneal syndrome)	42	3.9
Pleural infiltration	68	6.3
B. Pain syndrome related to direct tumor involvement due to lesions of nervous tissue	295	27.8
Peripheral nerve syndromes		
Due to paraspinal mass	16	1.5
Due to chest wall mass	30	2.8
Due to retroperitoneal mass other than paraspinal	13	1.2
Due to other soft tissue or bony tumor	23	2.1
Radiculopathy or cauda equina syndrome		
Due to vertebral lesion	64	5.9
Due to leptomeningeal metastases	2	0.2
Due to other intraspinal neoplasm	2	0.2
Painful polyneuropathy as a remote effect of neoplasm (paraneoplastic), diffuse infiltration or mononeuritis multiplex	4	0.4
Plexopathy		
Brachial plexopathy	49	4.5
Lumbosacral plexopathy	56	5.2
Sacral plexopathy	20	1.9
Cervical plexopathy	17	1.6
Cranial neuropathy		
Due to base of the skull tumor	4	0.4
Due to leptomeningeal metastases	7	0.6
Due to other bony of soft tissue cranial tumor	5	0.5
Pain due to central nervous system lesion		
Pain due to myelopathy (excluding pain related to bone, nerve root or cauda equina lesion)	5	0.5
Intracerebral lesion (only when pain is not due to intracranial hypertension)	6	0.6
C. Intracranial hypertension due to tumor	0	0
D. Headache, neck or back pain due to meningeal disease (does not include radiculopathy)	0	0
E. Pain syndromes related to therapy	110	10.2
Post-operative pain syndrome related to non-healing incision	6	0.6
Postradiotherapy syndromes		
Chronic enteritis	6	0.6
Damage to skin and subcutaneous tissue	34	3.2
Radiation fibrosis of brachial and lumbosacral plexus	17	1.6
Radiation myelopathy	7	0.6
Radiation induced peripheral nerve tumors	0	
Postchemotherapy syndromes		
Aseptic necrosis of bone	3	0.3
Steroid pseudorheumatism	2	0.2
Postchemotherapy polyneuropathy	7	0.6
Postoperative syndromes		
Postcraniotomy syndrome	2	0.2
Postmastectomy-postaxillary dissection	12	1.1
Postthoracotomy	16	1.5
Postradical neck dissection	7	0.6

Table 4 (*continued*)

	N	%
Postnephrectomy	0	
Postamputation (limbs)	6	0.6
Postinguinal dissection	0	
Headache related to cranial radiation therapy	1	0.1
Headache related to chemotherapy	1	0.1
F. Other (including symptoms unrelated to cancer or its treatment, to be specified)	71	6.6
G. Unknown	5	0.5

disease-related syndrome clusters. For example, patients with lung cancer were more likely to experience chest wall pain and pleural pains than other tumor types, and those with upper gastrointestinal tumors were much more likely to develop upper abdominal and/or back pain due to invasion of the rostral retroperitoneum.

The identified presence of breakthrough pain varied across countries. There was a relatively high rate of missing data on this item, and this too, varied across countries. A more detailed analysis of these data revealed that the main differences were between north-western European and a few other countries (USA, Canada, Australia, New Zealand) and the rest of the sample (Fig. 1).

All patients completed 10-point numeric scales for pain intensity. To clarify the factors that predicted clinically relevant levels of worst pain, the data were used to calculate cumulative odds ratios that describe the associations of different variables with mild, moderate and severe pain (see Section 2.3). In univariate analyses, the factors that were associated with higher pain intensity included the presence of breakthrough pain, somatic pain and neuropathic pain, age younger than 60 years, and lower performance status score; the presence of epigastric pain from an upper gastrointestinal neoplasm was associated with lower pain intensity (Table 7). The multivariate model that incorporated the variables that were determined to be significant univariately demonstrated that higher pain intensity was associated with the presence of breakthrough pain, somatic pain, younger age and lower performance status (Table 8).

4. Discussion

This survey represents the first effort to systematically describe cancer pain characteristics and syndromes in a large sample of patients who reside in different countries, the physicians response rate was only slightly over 50% in agreement with what is seen in most mailed questionnaire studies. Our data could also potentially enhance communication by suggesting the use of a common nomenclature applied to specific clinical phenomena by clinicians in

Table 5
Cancer pain syndrome classification

	N	%
S1 Base of the skull syndrome, headache due to calvarial, maxillary or mandibulary lesion	56	5.2
S2 Vertebral syndromes including sacrum	143	13.0
S3 Pelvis, long bones, direct infiltration of a joint	114	10.5
S4 Generalized bone pain due to multiple bone metastases due to bone marrow infiltration - expansion	122	11.4
S5 Chest wall pain from rib lesion	73	6.8
S6 Pathological fracture of long bone, vertebrae, pelvis, rib, other	54	5.0
S7 Esophageal mediastinal pain	30	2.8
S8 Shoulder pain from diaphragmatic infiltration, pain from distention of hepatic capsule, obstruction of biliary tract, left upper quadrant pain from splenomegaly	83	7.7
S9 Epigastric pain from pancreas or other upper abdominal neoplasm 'Midline rostral retroperitoneal syndrome'	85	7.9
S10 Diffuse abdominal pain from abdominal or peritoneal disease with obstruction without obstruction	68	6.3
S11 Suprapubic pain from infiltration of bladder, perineal pain from infiltration of rectum or perirectal tissue (including vagina)	105	9.7
S12 Obstruction of ureter	13	1.2
S13 Damage to oral mucous membranes, infiltration of skin and subcutaneous tissue	81	7.5
S14 Infiltration of muscle and fascia in the chest or abdominal wall, infiltration of muscle and fascia in the limbs	112	10.4
S15 Infiltration of muscle and fascia in the head and neck	56	5.2
S16 Retroperitoneal tissue infiltration excluding midline rostral retroperitoneal syndrome	42	3.9
S17 Pleural infiltration	68	6.3
S18 Peripheral nerve syndromes Due to paraspinal mass, chest wall mass, r etroperitoneal mass other than paraspinal, other soft tissue or bony tumor, peripheral polyneuropathy (paraneoplastic)	80	7.4
S19 Radiculopathy or cauda equina syndrome Due to vertebral lesion, leptomeningea1 metastases, other intraspinal neoplasm	70	6.5
S20 Plexopathy Cervical, brachial, lumbosacral, plexopathy	136	12.6
S21 Cranial neuropathy Due to base of the skull tumor, leptomeningeal metastases, other bony of soft tissue cranial tumor	16	1.5
S22 Pain due to central nervous system lesion Pain due to myelopathy (excluding pain related to bone, nerve root or cauda equina lesion) Intracerebral lesion (only when pain is not due to intracranial hypertension)	11	1.0
S23 Headache due to intracranial hypertension	0	0
S24 Neck, back pain or headache due to meningeal disease	0	0

different parts of the world. This analysis of nomenclature is particularly important when the phenomenon of interest – pain – has no objectively measurable correlate. This effort may suggest the utility of a checklist approach to syndrome identification, which could be adapted for clinical or research purposes in the future.

The survey acquired descriptive data from 58 pain specialists and 1095 of their patients in 24 countries. The patients were consecutively accrued based on a small number of inclusion and exclusion criteria. Although this method probably reduced the likelihood of selection bias at each site, the design as a whole was subject to both referral bias and observer bias. Specifically, all the investigators were members of the IASP and identified themselves as specialists in cancer pain. We asked to recruit patients with pain severe enough to require opioid medications. The data obtained from the patients referred to these clinicians cannot, therefore, be viewed as representative of the general cancer pain population. Moreover, this population had relatively severe illness, as demonstrated by a high prevalence of metastatic disease and a substantial proportion with relatively poor performance status. Thus, it is likely that this group of patients had relatively more severe pain problems than the general cancer population and the generalizability of the data should be interpreted in this light.

Although the data may illuminate a selected aspect of the cancer pain problem, they are relevant to that group of cancer patients experiencing significant pain problems after referral to IASP members with an interest in cancer pain.

The phenomenology of cancer pain syndromes in this study is comparable with previous clinical descriptions done at large referral cancer centers (Foley, 1979; Cherny and Portenoy, 1994; Caraceni, 1996) and can be an aid for both cancer pain experts and oncologist in their clinical practice.

The large sample in this survey allowed exploration of the various factors that may be associated with high levels of cancer pain. In the multivariate analysis, higher pain levels were associated with the presence of breakthrough pain, somatic pain, poorer performance status (usually signifying more advanced disease), and younger age. Neuropathic pain was a predictor of more intense pain in the univariate analyses. These relationships will be important to explore in future studies. Such studies should attempt to further standardize the definitions of phenomena like breakthrough pain and neuropathic pain as they are applied in the cancer population (Ventafridda and Caraceni, 1991), and determine the type of pain intensity measurement that is most useful in clarifying the critical distinctions among types of pain mechanisms (Jensen and McFarland, 1993). Future studies of these relationships would also benefit from longitudinal designs.

Fewer patients in this survey had multiple pains than in previous surveys (Grond et al., 1996; Twycross and Fairfield, 1982; Twycross et al., 1996) In contrast to one recent survey, which recorded multiple pains in 70–80% of patients (Grond et al., 1996), only about 25% of patients in the present survey had more than one pain. This difference is probably explained by methodological differences, particularly the emphasis on the 'worst pain' in the present survey. Although case definition according to 'worst pain'

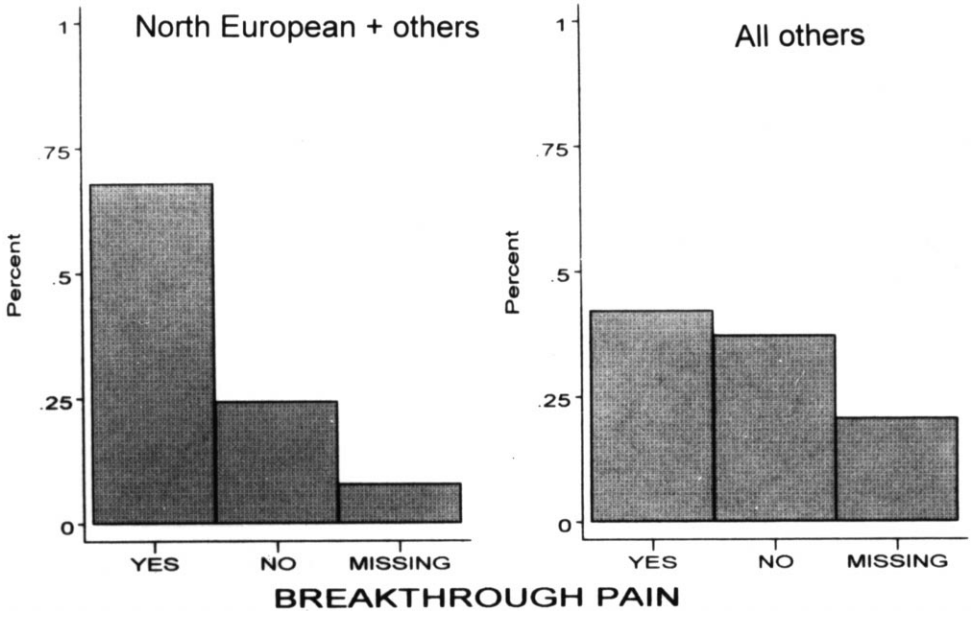

Fig. 1. Differences in the distribution of breakthrough pain identification across countries. North-western European countries (Scandinavian countries, Germany, The Netherlands and France) were grouped together with USA, Australia, New Zealand, and Canada. All other countries included in survey are in the comparison group.

Table 6
Frequency of pain syndromes according to cancer diagnosis

Syndrome[a]	Breast $N = 143$	Colon rectum $N = 103$	Upper GI tract $N = 104$	Head – neck $N = 111$	Leuk. – lymph. $N = 42$	Lung $N = 193$	Prostate $N = 65$	Uterus $N = 71$	Other $N = 243$
S1 Skull	2.1	1.9	1.9	21.6	0	4.6	1.5	0	6.1
S2 Vertebral	20.9	10.6	4.8	4.5	4.7	18.0	21.5	4.2	16.4
S3 Pelvis and long bones	12.5	17.4	0.9	6.3	11.9	8.8	26.1	4.2	11.1
S4 Generalized bone pain	25.3	0	0.9	5.4	14.2	10.4	40.0	0	11.3
S5 Chest wall	9.7	0.9	0	0.9	0	20.7	4.6	2.8	4.9
S6 Pathological fracture	8.3	1.9	0	0.9	0	7.7	3.0	0	8.2
S7 Esophageal mediastinal	0	0	13.4	3.6	2.3	3.6	0	0	1.6
S8 Liver capsule and biliary dist.	3.5	15.5	22.1	0.9	4.7	4.1	0	2.8	10.2
S9 Rostral retroperitoneal	0.7	3.8	64.4	0	7.1	1.0	1.5	0	2.4
S10 Abdominal	0	22.5	19.2	0	2.3	0	0	11.4	6.6
S11 Suprapubic-perineal	0	39.8	0	0	2.3	0	9.2	45.0	10.3
S12 Ureteral obstruction	0	0.9	0	0	0	0	3.0	4.2	2.8
S13 Oral and skin infiltration	9.0	3.8	0.9	32.4	9.5	1.5	0	2.8	7.4
S14 Chest and limb infiltration	14.6	6.8	4.8	1.8	14.2	16.5	4.6	12.6	10.2
S15 Head – neck muscle – fasciae	0	0	2.8	40.5	0	0.5	0	0	2.4
S16 Retroperitoneal (non S9)	0	2.9	6.7	0	9.5	0.5	6.1	9.8	6.5
S17 Pleural infiltration	6.9	2.9	0	2.7	0	22.8	3.0	0	2.4
S18 Peripheral neuropathy	6.2	3.8	1.9	2.7	7.1	13.4	4.7	2.8	10.7
S19 Radiculopathy	10.6	9.7	2.8	0.9	4.7	7.8	7.7	1.4	7.4
S20 Plexopathy	12.7	13.5	0.9	16.2	4.8	13.0	12.3	28.1	11.9
S21 Cranial neuropathy	1.4	0	0	8.1	0	1.5	0	0	0.8
S22 CNS	0	0.9	0	0	2.3	2.0	0	0	2.0

[a] Definitions in Table 5.

Table 7
Cumulative odds ratios (COR) and confidence intervals (CI) from univariate analysis for each of the two pain intensity cut-offs according to each of the variables[a]

Variable	COR 1st 1st cut off = pain ≥ 7	CI 1st	COR 2nd 2nd cut off = pain ≥ 5	CI 2nd
BKP yes	2.37	1.77–3.19	2.41	1.62–3.59
BKP no	1			
KPS ≤ 60	1.72	1.31–2.25	2.44	1.66–3.59
KPS > 60	1			
Somatic yes	1.22	0.91–1.63[b]	1.74	1.18–2.59
Somatic no	1			
Neuro yes	1.15	0.88–1.52[b]	1.71	1.13–2.60
Neuro no	1			
Syn 9 yes	0.53	0.34–0.84	0.33	0.20–0.57
Syn 9 no	1			
Age ≤ 60	1.35	1.03–1.78	0.97	0.65–1.44[b]
Age > 60	1			

[a] Only variables showing significant association with pain intensity are shown, BKP, breakthrough pain; KPS, Karnofsky performance status; Somatic, somatic pain; Neuro, neuropathic pain; Syn 9, epigastric pain due to pancreas or other upper abdominal neoplasm.
[b] Not significant.

may diminish the reports of multiple pains, it is reasonable given evidence that worst pain identifies the most clinically relevant pain syndromes (Cleeland, 1984; Cleeland et al., 1988, 1994; Serlin et al., 1995). Another reason for the observed difference can be that in this study the information was physician recorded rather than patient recorded.

The identification of transitory pains (breakthrough pains) in a high proportion of patients replicates previous surveys (Banning et al., 1991; Mercadante et al., 1992; Bruera et al., 1995; Portenoy and Hagen, 1990). Breakthrough pain is an important phenomenon, which may increase patient distress and reduce the responsiveness to opioid therapy (Bruera et al., 1989, 1995; Mercadante et al., 1992, 1994). Additional studies of breakthrough pain phenomenology and impact are needed.

Table 8
Cumulative odds ratios (COR) and confidence intervals (CI) from multivariate analysis for each of the two pain intensity cut-offs according to the independent variables[a]

Variable	COR 1st 1st cut off = pain ≥ 7	CI 1st	COR 2nd 2nd cut off = pain ≥ 5	CI 2nd
BKP yes	2.08	1.52–2.85	1.88	1.26–2.81
BKP no	1			
KPS ≤ 60	1.63	1.19–2.23	2.29	1.51–3.47
KPS > 60	1			
Somatic yes	0.92	0.65–1.30[b]	1.61	1.05–2.46
Somatic no	1			
Age ≤ 60	1.56	1.14–2.14	1.21	0.80–1.83[b]
Age > 60	1			

[a] BKP, breakthrough pain; KPS, Karnofsky performance status; Somatic, somatic pain.
[b] Not significant.

The many investigators in the present survey did not add any cancer-related syndromes to the checklist. This suggests that it was adequately comprehensive. Although some syndromes were not encountered, the biases in the sample selection must be considered in interpreting these data. For example, the absence of pain due to intracranial hypertension may result from the lack of referral of such problems to pain specialists. Further study in a general population of cancer patients is needed to obtain an unbiased accounting of cancer pain syndrome phenomenology.

Notwithstanding, the data suggest that there may be important disease-specific syndrome clusters. This finding is consistent with clinical experience and smaller surveys of selected cancer populations (Foley, 1979; Greenberg et al., 1981; Kori et al., 1981; Arner and Arner, 1985; Jaeckle et al., 1985; Bruera et al., 1989; Vecht et al., 1989, 1992; Vecht, 1990; Portenoy, 1992; Portenoy et al., 1992, 1994; Cheng et al., 1993; Cherny and Portenoy, 1994; Caraceni, 1996; Caraceni and Portenoy, 1996) A large survey also demonstrated the importance of site of the tumor as a determinant of pain syndromes (Grond et al., 1996). Surveys using the checklist in targeted cancer populations may be able to further elucidate syndrome clusters associated with the common tumor types.

Based on syndrome prevalence, these data suggest that a parsimonious syndrome grouping (Table 5) may be useful to simplify analysis. Although not identified in this survey, several syndromes might be added to this list pending additional study. For example, it would be reasonable to add headache due to intracranial hypertension and headache, neck pain or back pain due to leptomeningeal disease, and to separate painful polyneuropathy from other peripheral nerve pains, based on the prevalence of such disorders in the literature. These syndrome groupings are not intended to be definitive, but rather, should provide the impetus for the evolution of empirically-based syndrome lists that can simplify patient assessment in the clinical and research settings.

The possibility of systematic differences in labeling of specific syndromes across countries cannot be adequately answered by this survey due to the limited number of patients per country. The possibility that nomenclature differences do exist is suggested by the variability of observer rated prevalence of breakthrough pain. This variability could reflect either differences in the application of the term in labeling a clinical phenomenon or differences in the degree to which the phenomenon of fluctuating pain is even recognized as present. Also, although unlikely, we cannot disregard the potential effect of systematic patient selection bias in different countries. Other multinational studies are needed to determine the nature of these differences and clarify the degree to which the prevalence of other phenomena, including syndrome labeling, may vary according to local norms in the application of terms.

The inferred pathophysiologies identified in the present study were similar to the large survey of Grond et al., 1996.

Among the 2266 patients in Grond's survey, somatic pains occurred in 80% (from a bone lesion in 35% and from soft tissue or myofascial processes in 45%), and visceral and neuropathic mechanisms occurred in 33 and 34%, respectively. In an earlier survey of patients with far advanced disease (Twycross and Fairfield, 1982), pain was caused by lesions of the bone in 31%, viscera in 31%, nerve in 31%, and soft tissue in 31%.

The management of pain is a critical issue in the care of patients with cancer. Pain is ultimately experienced by large majority of patients with incurable solid tumors and pain relief is an imperative throughout the course of the disease. Dissemination of the knowledge and resources necessary to manage pain must continue to be given high priority, particularly in developing countries that lack resources for sophisticated cancer prevention and control programs. More research in cancer pain is needed to improve current techniques because even specialist-based treatment programs cannot completely relieve pain at the end of life in as many as 20% of patients (De Conno et al., 1996). This research should identify, using anatomical, pathophysiological or mechanistic approaches, groups of patients at risk for unrelieved pain to be able to focus management and research efforts on the improvement of both assessment and management of this important problem.

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