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ORIGINAL ARTICLE

Revisiting classification of pain from bone metastases as mild, moderate, or severe based on correlation with function and quality of life

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Abstract

Purpose The objective of our study was to determine the optimal cut points for classification of pain scores as mild, moderate, and severe based on interference with function and quality of life (QOL).

Methods We evaluated 822 patients who completed the Brief Pain Inventory (BPI) and/or the European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire Core 30 (QLQ-C30) prior to receiving repeat radiation therapy for previously irradiated painful bone metastases. Optimal cut points for mild, moderate, and severe pain were determined by the MANOVA that yielded the largest F ratio for the between category effect on the seven interference items of BPI and the six functional domains of QOL (physical, role, emotional, cognitive, social functioning, and global QOL) as indicated by Pillai's Trace, Wilk's λ, and Hostelling's Trace F statistics.

Results For BPI and for QOL domains separately, the two largest F ratios for Wilk's λ, Pillai's Trace, and Hotelling's Trace F statistics were from the cut points 4, 8 and 6, 8. When combining both, the optimal cut points were 4, 8 with 1–4 (mild), 5–8 (moderate), and 9–10 (severe). With this classification, the mean scores of all the seven interference items in BPI and the six functional domains were all highly statistically

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different. Patients with severe pain survived significantly shorter than those with mild and moderate pain ($p < 0.0001$). *Conclusion* Our analysis supports the classification of pain scores as follows: 1–4 as mild pain, 5–8 as moderate pain, and 9–10 as severe pain. This may facilitate conduct of future clinical trials.

Keywords Quality of life · Functional interference · Bone metastases · Re-irradiation · Pain severity · Survival

Introduction

Pain is common and distressing in patients with bone metastases. Uncontrolled pain can disrupt and interfere with daily functioning and quality of life (QOL) [1]. Valid pain assessment tools are required for clinicians to adequately evaluate pain intensity and the effectiveness of therapeutic interventions for pain management. Commonly used tools such as the Brief Pain Inventory (BPI) [2] often use a 0–10 numeric rating scale (NRS) or a 10-cm line visual analogue scale (VAS). These tools have good sensitivity and facilitate statistical analyses. However, for simplicity, patients may prefer the use of mild, moderate, and severe categories when communicating with their clinicians [3].

Current clinical practice guidelines such as the World Health Organization pain analgesic ladder [4] are based on categorization of pain as mild, moderate, or severe. Others, including the American Pain Society Pain Guideline [5] and National Comprehensive Cancer Network guideline [6], use both numerical pain scales and categorical scales. Classification of pain intensity into three categories may be useful for several reasons: to guide clinical decision, to facilitate dialogue between patients and the health-care providers, and to measure outcomes in clinical trials [7].

Studies have been conducted to establish optimal cut points on a numerical scale for classification of pain as mild, moderate, or severe. This was first proposed by Serlin et al. in 1995 using a novel multivariate statistical approach which was shown to correlate with functional interference reported by patients using the BPI instrument. The analysis included data from greater than 1800 patients with cancer-related pain in four countries (USA, the Philippines, France, and China) and found that the optimal cut points for mild and moderate pain were 4 and 6, respectively [8]. Other investigators repeated the same analysis using different populations and sources of pain. However, the pain severity cut points have been inconsistent across studies with the upper boundary for mild and moderate pain ranging from 3 to 5 and 6 to 8, respectively. The previous studies primarily correlated the pain categorization with interference in daily functioning [9, 10]. In addition, pain severity may be associated with poor outcomes [1].

To explore this further, we ought to determine the optimal cut points for categorization of pain as mild, moderate, and severe in patients with pain from bone metastases by assessing its impact on daily functioning and QOL. The secondary objective of our study was to investigate if severity of pain correlated with survival.

Methods

We analyzed the database of NCIC Clinical Trials Group (CTG) Symptom Control.20 (SC.20). The details of the study have been reported before [11, 12]. Patients completed the BPI [2] and/or the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) [13] at baseline. The BPI includes an 11-point scale from 0 to 10 to assess the severity of pain. Patients were asked to score their worst pain in the past 3 days. The BPI also administers questions on a scale of 0 to 10 pertaining to the functional interference in general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life [2].

The EORTC QLQ-C30 contains five multiple-item subscales (physical, role, emotional, cognitive, and social functioning), six single-item symptom scales (sleep disturbance, constipation, diarrhea, dyspnea, appetite loss, and financial issues), three multiple-item symptom scales (fatigue, pain, and nausea), and a two-item global health status scale. All items are rated using a 4-point Likert type scale from 1 (not at all) to 4 (very much), with the exception of the two-item global health status scale, which is rated from 1 (very poor) to 7 (excellent). Each subscale is linearly converted to a score ranging from 0 to 100, where a higher score indicates better functioning for the functional scales or greater severity of symptoms for the symptom scales [13]. We employed six functional domains of QOL (physical, role, emotional, cognitive, social functioning, and global QOL) as outcome variables in this study.

Statistical analysis

To determine the optimal cut points for classification of mild, moderate, and severe pain, we followed the statistical methods described by Serlin et al. [8]. Different cut points of BPI were used to identify the cutoffs that best differentiate among the three groups (mild vs. moderate vs. severe) based on the worst pain collected at baseline. Patients were divided into three groups according the following cutoff as determined with at least 10 % of patients in each group for the possible cutoff for mild, moderate, and severe pain categories:

a. ≤4 vs. 5 vs. >5

Table 1 The mean and standard deviation (SD) for each of the baseline seven interference items and the six functional QOL domains

BPI interference item	Mean (SD)–number
General activity	5.91 (2.83)–775
Mood	4.49 (2.90)–775
Walking ability	5.58 (3.22)–772
Normal work	6.34 (3.00)–769
Relations with others	3.31 (2.99)–776
Sleep	4.33 (3.15)–777
Enjoyment of life	5.36 (3.23)–775
QOL functional domain	Mean (SD)–number
Physical	49.94 (23.16)–567
Role	40.26 (30.83)–568
Emotional	64.65 (23.81)–560
Cognitive	71.96 (24.95)–567
Social	57.62 (30.94)–562
Global	45.86 (21.87)–559

b. ≤4 vs. 5, 6 vs. >6
c. ≤4 vs. 5, 6, 7 vs. >7
d. ≤4 vs. 5, 6, 7, 8 vs. >8
e. ≤5 vs. 6 vs. >6
f. ≤5 vs. 6, 7 vs. >7
g. ≤ 5 vs. 6, 7, 8 vs. >8
h. ≤6 vs. 7 vs. >7
i. ≤6 vs. 7, 8 vs. >8
j. ≤7 vs. 8 vs. >8

Table 2 Analysis with baseline BPI and QOL for the possible cut points

Cut points	Wilk's λ, F	Pillai's Trace, F	Hotelling's Trace, F
BPI			
CP4, 5	7.88	7.63	8.13
CP4, 6	10.60	10.11	11.09
CP4, 7	12.34	11.67	13.02
CP4, 8	12.75	12.08	13.42
CP5, 6	9.46	9.11	9.83
CP5, 7	11.16	10.64	11.67
CP5, 8	12.01	11.44	12.59
CP6, 7	11.18	10.67	11.69
CP6, 8	12.94	12.26	13.62
CP7, 8	12.17	11.59	12.76
QOL functional domain			
CP4, 5	4.76	4.71	4.81
CP4, 6	5.87	5.74	5.99
CP4, 7	8.15	8.00	8.31
CP4, 8	12.03	11.66	12.41
CP5, 6	4.55	4.49	4.62
CP5, 7	6.68	6.57	6.79
CP5, 8	9.88	9.51	10.26
CP6, 7	6.60	6.47	6.72
CP6, 8	10.40	9.99	10.82
CP7, 8	10.38	9.95	10.82

The set of seven interference items from the BPI questionnaire as outcomes (treated as a multivariate normal variable) was analyzed using the multivariate analysis of variance (MANOVA, SAS proc glm). Optimal cut points for mild, moderate, and severe pain were determined by the MANOVA among pain severity categories that yielded the largest F ratio for the between category effect on the seven interference items as indicated by Pillai's trace, Wilk's λ, and Hostelling's trace F statistics [8, 14]. Similar analysis with six functional domains of QOL (physical, role, emotional, cognitive, social

Table 3 Baseline patient characteristics for the three groups

	Mild		Moderate		Severe		p value
	#	(%)	#	(%)	#	(%)	
Total	103	(100)	549	(100)	170	(100)	
Median age (years)	67.2		64.9		64.4		0.89*
Gender							
Female	23	(22)	239	(44)	75	(44)	0.002
Male	80	(78)	310	(56)	95	(56)	
Primary cancer site							
Breast	13	(13)	161	(29)	40	(24)	0.003
Lung	23	(22)	124	(23)	40	(24)	
Prostate	44	(43)	139	(25)	40	(24)	
Others	21	(20)	116	(21)	46	(27)	
Unknown	2	(2)	9	(2)	4	(2)	
Karnofsky performance status							
Unknown	3	(3)	6	(1)	1	(1)	<0.0001
50–60	11	(11)	105	(19)	63	(37)	
70–80	53	(51)	304	(55)	91	(54)	
90–100	36	(35)	134	(24)	15	(9)	
Site of painful bone lesion							
Pelvis/hips	36	(35)	200	(36)	59	(35)	0.60
Lumbosacral spine	19	(18)	94	(17)	36	(21)	
Superficial bones	18	(17)	65	(12)	17	(10)	
Upper limbs	9	(9)	49	(9)	23	(14)	
Thoracic spine	9	(9)	62	(11)	12	(7)	
Lower limbs	5	(5)	28	(5)	10	(6)	
Thoracolumbar spine	5	(5)	37	(7)	7	(4)	
Cervical spine	1	(1)	6	(1)	3	(2)	
Cervicothoracic spine	1	(1)	5	(1)	2	(1)	
Other	0	(0)	3	(1)	0	(0)	
Unknown	0	(0)	0	(0)	1	(1)	

*p value from ANOVA test, all others are from chi-square test

functioning, and global QOL) as outcome variables was performed with QOL transformed in a range of 0 to 100.

We then regrouped the patients based on the results of the optimal cut points from both analyses. Chi-square and ANOVA tests were used to test the difference among the three groups in terms of BPI, QOL, and other baseline factors [15], while log-rank test and Cox regression model were used to test the difference in overall survival among the three groups adjusted for prognostic factors of the population [16]. All analyses were performed using the Statistical Analysis System (SAS; SAS Institute, Cary, NC).

Results

Of the 850 patients entered onto the SC.20 trial, 822 patients completed BPI and/or six functional domains of QOL at baseline. There were 337 female and 485 male patients with a median age of 65 years old (range 18 to 94). Their median KPS was 80 (range 50 to 100). The most common primary cancer sites were the breast, lung, and prostate. The mean baseline worst pain score was 7.0 (range 2 to 10). The mean and standard deviation (SD) of each of the baseline seven interference item scores and the six functional QOL domains are listed in Table 1.

Table 2 lists the analyses on the potential cut points based on the BPI and QOL domains. For BPI, the two largest F ratios for Wilk's λ, Pillai's Trace, and Hotelling's Trace F statistics were from the cut points (CP 4, 8 and CP 6, 8) and they were 12.75, 12.08, 13.42 and 12.94, 12.26, 13.62, respectively. Similarly, for QOL domains, the two largest F ratios for Wilk's λ, Pillai's Trace, and Hotelling's Trace F statistics were again from the cut points (CP 4, 8 and CP 6, 8) and they were 12.03, 11.66, 12.41 and 10.40, 9.99, 10.82, respectively. When combining both, the optimal cut point was CP 4, 8. Therefore, the most optimal cutoff based on BPI and EORTC QLQ C30 was 1–4 (mild), 5–8 (moderate), and 9–10 (severe).

We regrouped the three categories of the patients in Table 3. There were 103, 549, and 170 patients with mild, moderate, and severe pain, respectively. Post hoc analyses demonstrated that patients with mild pain were more likely male ($p = 0.002$), with a primary diagnosis of prostate cancer ($p = 0.003$), and had a better KPS ($p < 0.0001$). The mean and SD of each of the seven interference items score from the baseline BPI for each of the three groups were all highly statistically different (Table 4). The ratio of the mean score from moderate/mild pain category for the seven interference item ranged from 1.4 (normal work) to 1.8 (relations with others). The ratio of the mean score from severe/mild pain category ranged from 1.8 (normal work) to 2.6 (relations with others), while the ratio for severe/moderate pain category ranged from 1.3 (walking ability, normal work, and sleep) to 1.5 (relations with others). Relations with others appear to be most affected proportionately from mild to moderate to severe pain category.

The mean and SD of each of the six QOL functional domains score from the baseline EORTC QLQ C30 for each of the three groups were all highly statistically different (Table 5). The ratio of the mean score from moderate/mild pain category was only 0.96 and 0.98 for emotional and cognitive subgroups but decreased to 0.78 (severe/mild), 0.81 (severe/moderate) and 0.78 (severe/mild), 0.79 (severe/moderate), respectively. Besides the emotional and cognitive subgroups, for the remaining four QOL domains, the ratio of the mean score from moderate/mild pain category ranged from 0.68 (role) to 0.89 (global). For all the six QOL domains, the ratio of the mean score from severe/mild pain category ranged from 0.41 (role) to 0.78 (emotional and cognitive), while the ratio for severe/moderate pain category ranged from

Table 4 Mean and standard deviation (SD) of the seven interference items score from the baseline BPI among the three groups

BPI interference item	Mild pain Mean (SD) *N*	Moderate pain Mean (SD) *N*	Severe pain Mean (SD) *N*	*p* value (ANOVA)
General activity	3.65 (2.65) 96	5.73 (2.56) 517	7.85 (2.53) 162	<0.0001
Mood	2.76 (2.23) 97	4.33 (2.78) 517	6.12 (2.84) 161	<0.0001
Walking ability	3.45 (2.85) 97	5.52 (3.05) 513	7.04 (3.19) 162	<0.0001
Normal work	4.41 (3.13) 96	6.17 (2.82) 511	8.04 (2.59) 162	<0.0001
Relations with others	1.77 (2.14) 97	3.17 (2.89) 517	4.69 (3.19) 162	<0.0001
Sleep	2.70 (2.59) 97	4.31 (2.99) 519	5.40 (3.50) 161	<0.0001
Enjoyment of life	3.51 (2.86) 97	5.15 (3.08) 517	7.14 (3.09) 161	<0.0001

Table 5 Mean and standard deviation (SD) of the six baseline QOL functional domains score among the three groups

QOL functional domain	Mild pain Mean (SD) *N*	Moderate pain Mean (SD) *N*	Severe pain Mean (SD) *N*	*p* value (ANOVA)
Physical	67.26 (20.91) 65	51.20 (21.57) 382	36.56 (21.85) 120	<0.0001
Role	60.77 (29.67) 65	41.58 (29.32) 382	25.07 (28.72) 121	<0.0001
Emotional	69.53 (20.01) 63	67.05 (22.34) 378	54.46 (27.30) 119	<0.0001
Cognitive	76.92 (21.18) 65	75.02 (23.21) 381	59.64 (28.20) 121	<0.0001
Social	72.14 (25.21) 64	60.91 (30.18) 379	39.36 (28.43) 119	<0.0001
Global	55.16 (21.14) 63	49.14 (18.80) 377	30.53 (24.14) 119	<0.0001

0.60 (role) to 0.81 (emotional). Role (0.41 for severe/mild, 0.60 for severe/moderate, and 0.68 for moderate/mild), global (0.55 for severe/mild and 0.62 for severe/moderate), social (0.55 for severe/mild and 0.65 for severe/moderate), and physical (0.54 for severe/mild, 0.71 for severe/moderate, and 0.76 for moderate/mild) subgroups appear to be most affected proportionately from mild to moderate to severe pain category. Emotional and cognitive subgroups had the least impact relatively.

The median survival for patients with mild, moderate, and severe pain was 10.6, 10.5, and 4.9 months, respectively. Patients with severe pain survived significantly shorter than those with mild and moderate pain ($p < 0.0001$), and remained associated with worse overall survival ($p < 0.0001$) after adjusting baseline prognostic factors (Table 6) (Online Resource 1).

Discussion

Previous work indicated for cancer-related pain the optimal upper cut point for mild and moderate pain was 4 and 6 and a nonlinear relationship between pain severity and functional interference exists, i.e., there is a certain threshold level above which pain has a significant impact on function [8]. Li et al. repeated the study in 199 patients with painful bone metastases referred for palliative radiotherapy, again employing BPI [9]. Their result concurred with that of Serlin et al. that mild pain was best categorized as scores between 1 to 4, moderate pain as 5 and 6, and severe pain as 7 to 10. However, in another study of 160 patients with bone metastases, Paul et al. defined 1–4 as mild, 5–7 as moderate, and 8–10 as severe pain [10]. The three studies all employed BPI as the pain measurement tool. Serlin et al. included patients from both inpatient and outpatient settings with cancer-related pain from different etiologies in four different countries [8]. Li et al. [9] and Paul et al. [10] recruited outpatients with painful bone metastases in Toronto, Canada, and Northern California, USA, respectively.

Our current study is the first paper to utilize both BPI and patient self-reported QOL outcomes to categorize pain severity using the database of a multinational study that enrolled patients with painful bone metastases. Our results suggest that optimal cut points would be 4 and 8 with 1–4 as mild pain, 5–8 as moderate pain, and 9–10 as severe pain. With this classification, post hoc analyses confirmed that the mean scores of the seven interference items in BPI and the six functional QOL domains were all highly statistically different in the three categories of pain. In patients with severe pain, in addition to

Table 6 Multivariate analysis of pain intensity groups with overall survival

Factor	Hazard ratio	95 % C.I.	*p* value (Wald test)
Pain severity			
Mild (1–4)	0.94	0.68–1.30	0.72
Moderate (5–8)	1		
Severe (9–10)	1.79	1.43–2.24	<0.0001
Gender			
Male	1.21	0.93–1.57	0.15
Female	1		
Karnofsky Performance Scale			
50–60	2.22	1.62–3.03	<0.0001
70–80	1.65	1.26–2.17	0.0003
90–100	1		
Primary site			
Prostate	1.44	0.96–2.15	0.075
Lung	3.75	2.67–5.26	<0.0001
Others	2.62	1.85–3.72	<0.0001
Breast	1		

inferior function and QOL, their survival was also worse when compared with patients with mild and moderate pain. This group of patients with severe pain or in pain crisis would require urgent attention to get the pain relief. In future clinical trials, if the outcome measures relate to functional interference and QOL, our findings suggest that consideration should be made to stratify according to the pain severity.

Wang et al. enrolled 216 patients with cancer-related pain who completed the BPI and SF-36 [17]. The SF-36 focuses on eight different domains of health-related QOL: (1) physical functioning, (2) role limitations due to physical problems, (3) social functioning, (4) bodily pain, (5) general mental health, (6) role limitations due to emotional problems, (7) vitality, and (8) general health perceptions. The authors grouped their patients in terms of the pain severity based on the Serlin et al. classification with none as 0, mild 1–4, moderate 5–6, and severe 7–10. The functional health and well-being of patients with no or mild pain was significantly less impaired than that of patients with moderate or severe pain. The impairment of patients with moderate and severe pain did not differ. The employment of moderate pain as 5–8 and severe pain as 9–10 in our study was able to detect the statistically significant difference in the two groups in both functional and QOL domains. The population studied in SC.20 received re-irradiation, thus had previous experience which may influence their response. The other series had de novo pain which may influence perception and of course likely to be earlier in disease natural history.

Another alternative to explore the optimal cut points would be to ask the patients to rate their pain simultaneously on both a numerical scale of 0–10 (0 = no pain, 10 = worst pain possible) and a categorical scale: none, mild, moderate, and severe. A study enrolling 217 patients in an outpatient palliative radiotherapy clinic with this strategy reported their patients scored their pain as mild if pain was 1–4, moderate if pain was 5–7, and severe pain 8–10 [18]. The result was similar to that reported by Paul et al. [10]. More research is required to determine if correlation of the functional and QOL impairment or patient's perception would provide optimal cut points for pain severity.

We also did sensitivity analyses of grouping the possible combinations of cut points 4, 6 and 4, 7 among the three groups (mild, moderate, and severe pain categories) in terms of their correlation with functional and QOL domains and survival (results not shown). The cut points 4, 8 provide the largest difference in the mean scores of all the BPI and QOL domains for the three pain groups and the worst survival for the severe pain category.

Our findings support the categorization of cancer-related pain into severity ratings in patients with bone metastases in studies testing palliative interventions. This categorization will also help in the design of pain assessment instruments. The numerical 0–10 scale, though proven reliable and valid, can be further improved by descriptors on the scale such as 0 = no pain, 1–4 represent mild pain with little impact, 5–8 represent moderate pain with intermediate impact, and 9–10 represent severe pain with significant impact on both function and QOL. By including these descriptors to the numbers on the scale, pain ratings may be more meaningful to both patients and clinicians in both research and practice settings. Future research concerning the potential psychometric improvements in terms of reliability and validity of the pain rating scales that use such descriptors is warranted [19].

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