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Functional interference clusters in cancer patients with bone metastases: A secondary analysis of RTOG 9714

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Abstract

Purpose—To explore the relationships (clusters) among the functional interference items in the Brief Pain Inventory (BPI) in patients with bone metastases.

Methods—Patients enrolled in the RTOG 9714 bone metastases study were eligible. Patients were assessed at baseline, 4, 8, and 12 weeks after randomization for the palliative radiotherapy with the BPI which consists of seven functional items: general activity, mood, walking ability, normal work, relations with others, sleep and enjoyment of life. Principal component analysis with varimax rotation was used to determine the clusters between the functional items at baseline and the follow- up. Cronbach's alpha was used to determine the consistency and reliability of each cluster at baseline and follow-up.

Results—There were 448 male and 461 female patients with a median age of 67 years. There were two functional interference clusters at baseline which accounted for 71% of the total variance. The first cluster (physical interference) included normal work and walking ability which accounted for 58% of the total variance. The second cluster (psychosocial interference) included relations with others and sleep which accounted for 13 % of the total variance. The Cronbach's alpha statistics were

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0.83 and 0.80 respectively. In responders, the functional clusters changed at week 12 but persisted through week 12 in non-responders.

Conclusion—Palliative radiotherapy is effective in reducing bone pain. Functional interference component clusters exist in patients treated for bone metastases. These clusters changed over time in this study; possibly attributable to treatment. Further research is needed to examine these effects.

Keywords

Bone metastases; palliative radiotherapy; cluster; functional interference; Brief Pain Inventory; principal component analysis

Introduction

Bone metastases are common in patients with breast, prostate and lung cancers. Bone metastases cause pain and skeletal related events such as hypercalcemia, pathological fracture and spinal cord compression. Moreover functional interference affects many patients with bone metastases (1). The Brief Pain Inventory (BPI) is a multidimensional instrument developed by Cleeland and colleagues. It is by far the most frequently used multiple-item measure of pain in cancer research. The BPI measures functional interference in addition to pain. The dimensions of functional interference the instrument measures include: general activity, normal work, walking ability, mood, sleep, relations with others and enjoyment of life (2,3).

Patients with advanced cancer often present with multiple symptoms that may or may not be interrelated. Recent publications show that patients have an average of 11 – 13 concurrent symptoms (4,5). It has been reported that symptom complexes or clusters might occur. The term `symptom cluster' was first coined by Dodd et al in their work with pain, fatigue and sleep disturbances (6). They defined symptom clusters as three or more concurrent symptoms that are related to each other but may or may not have the same etiology. Kim et al described symptom clusters as two or more symptoms that are related to each other, occur together, are a stable group and are relatively independent of other clusters (7). The primary objective of this secondary study was to explore the relationships (clusters) among the functional items in BPI. Palliative radiotherapy has been shown to be very effective in treating painful bone metastases. The overall pain response rate can be over 60 % (1). The secondary objective was to determine whether these clusters (if any) changed with palliative radiotherapy.

Methods

Pain and functional interference assessment

The Brief Pain Inventory (BPI) worst pain score is an 11-point (0–10) Likert scale used to assess pain with 0 indicating no pain and 10 indicating unimaginable pain. Pain response was categorized as the following: 1) complete response, post-treatment pain score of 0; 2) partial response, post-treatment improvement of at least 2 points; 3) stable response, post-treatment pain score within 1 point of the initial pain score, or 4) progressive response, a post-treatment increase of at least 2 points. Patients with complete or partial response were considered responders; patients with stable or progressive response were considered non-responders. The BPI contains seven items scaled on a similar 11-point Likert scale to assess functional interference. Higher scores indicate increased functional interference.

Patient Population

The Radiation Therapy and Oncology Group (RTOG) and the North Central Cancer Treatment Group (NCCTG) conducted a randomized phase III trial with breast or prostate cancer patients with bone metastases (RTOG 9714) (8). Eligible patients had moderate or severe pain, as indicated by a BPI worst pain score of ≥5 or narcotic medication with a daily oral morphine equivalent dose of at least 60 mg if pain scores less than 5. Patients were randomized between treatment with a single fraction of 8 Gy and 30 Gy in 10 fractions. The Karnofsky performance status of the enrolled patients was at least 40 with an estimated life expectancy of at least 3 months. Patients were excluded if there was prior radiation therapy or palliative surgery to the planned radiation treatment site, pathological or impending fracture, spinal cord or cauda equina compression. Worst pain and functional interference scores were assessed using BPI at baseline, 4, 8 and 12 weeks post randomization.

RTOG 9714 concluded both a single 8 Gy and 30 Gy in 10 fractions were equivalent in terms of pain and narcotic relief at 3 months and were tolerated with few adverse effects. There were no significant differences in gender or marital status with reference to the response to palliative radiotherapy. Therefore in this secondary study adjustments for treatment or gender differences were not evaluated.

Statistical Methods

Spearman's correlation coefficients were calculated to compare the association between the baseline BPI functional item scores. Principal component analysis (PCA) with varimax rotation was used to determine relationships between the functional items at baseline for all patients, and at subsequent follow-up for non-responders and responders. The highest factor score determined the assignment of a functional item to a component. Functional items with high factor scores (>0.40) in multiple components were not assigned. Components with at least two factors were retained. The final communality details the percent of variance of each BPI item that was explained by the retained components. Cronbach's alpha was used to determine the internal consistency and reliability of each component at baseline and follow-up. Spearman's correlation coefficients were calculated to compare the association between the functional components and treatment response at each follow-up period. A general linear mixed model was used to determine overall trends in the treatment effect on the functional component scores, at the 0.05 significance level (9). All data were analyzed using SAS (version 9.1 for Windows, SAS institute, Cary, NC).

Results

All eligible patients enrolled in RTOG 9714 were analysed. There were 448 male and 461 female patients with a median age of 67 years (range 37–92). The majority of the patients had a KPS of 70 or 80 (54%), did not receive bisphosphonates (76%), had a solitary bone metastasis (57%), were treated at a weight bearing site (56%), and had a marital partner (59%) (Table 1). The distribution of the baseline BPI worst pain and functional item scores is listed in Table 2. The median worst pain score was 8 (range 0–10). The median functional item scores ranged from 3 to 8. Of the seven functional interference items, normal work and relationship with others were the highest and lowest scored items respectively. The correlation between each BPI item was highly significant at baseline ($p < 0.0001$). The correlation between normal work and general activity was the highest (0.69); whereas the correlations between worst pain and relations with others and sleep and walking ability were the lowest (0.28) (Table 3).

Principal components which had eigenvalues greater than 1 or explained more than 10% of the variance were retained (Table 4). The two baseline clusters accounted for 71% of the total variance. The first cluster (physical interference) included normal work and walking ability which accounted for 58% of the total variance. The second cluster (psychosocial interference) included relations with others and sleep which accounted for 13% of the total variance. The internal reliabilities of each cluster based on the Cronbach's alpha statistic were 0.83 and 0.81, respectively. Final communality estimates ranged from 0.62 for sleep to 0.78 for normal work. In responders, the functional interference clusters were reduced to a single item at week 12

(Table 5a). In non-responders, the functional interference clusters persisted through week 12 (Table 5b). Both functional component scores were significantly correlated with treatment response at each follow-up assessment—4, 8, and 12 weeks. There were significant differences in functional component scores between responders and non-responders, adjusting for time of assessment (Table 6).

Discussion

Bone metastases cause pain and functional interference in patients with advanced cancer. The BPI developed by Cleeland and colleagues is designed to measure the subjective intensity of pain and functional impairment caused by pain (2,3). Employing the concept of symptom clusters, we explored the relationships (clusters) among the functional items in BPI and examined if they changed following palliative radiotherapy.

Our analysis revealed two functional interference clusters at baseline: the physical interference (normal work and walking ability) and psychosocial interference (relations with others and sleep). These two functional interference clusters changed at week 12 in responders but persisted through week 12 in non-responders.

Previous studies presented similar clusters. Saxena et al in the validation of the Hindi BPH identified a factor comprised of interference with enjoyment of life, mood and relationship with others (10). They classified this factor as mood-related interference. Activity-related interference was the other factor identified and included interference with work, walk and general activity. Sleep did not load onto any of the two factors. This result was consistent with a previous study reported by Cleeland et al that the interference factor can further be decomposed into activity-related and mood-related dimensions. Klepstad and colleagues in validating the Norwegian BPI further confirmed these two factors (11). The first one was the interference items describing the influence of pain on physical functions (general activity, walking ability and normal work), and the other was the items on psychological related functions (mood, relations with other people and enjoyment of life) and sleep. The authors postulated the interference on physical symptoms from pain is probably caused by a direct limiting capacity on physical function. The influence from pain on psychological symptoms could be related to a combination of the physical suffering, and the patient's interpretations of pain in the context of malignant disease. Contrary to previous results; however our analysis indicated that sleep was a psychosocial interference factor. A confirmatory factor analysis using an independent cancer centre data set will be used to further understand this phenomenon.

Our study further examined the interactions of the functional interference clusters with radiation treatment. The functional items changed with time from one component to another component. This has been discussed in the literature as cluster stability which can be conceptualized as specific clusters that exist in different populations or those influenced by treatments (12). Symptoms may participate in different clusters depending on severity and treatment (13,14). A specific symptom in a cluster (possibly the one influenced most by treatment) may be a mediator, and the relationships between the cluster symptoms may be indirect. The type of pain, primary site, stage of disease and symptom meaning may also influence cluster composition (15,16). Symptoms change with disease course and treatment; clusters may change as well. In our study, bone pain may have influenced (directly or indirectly) the functional interference clusters by change in severity after radiotherapy, or functional interference severity may determine greater cluster variability.

Kirkova and Walsh proposed to determine the presence of a cluster, perhaps at least 75% of the symptoms within a cluster should be present, including the most prominent or important symptom (that with the greatest weight from factor analysis, or the dependant variable in multiple regression correlations) (12). We have chosen the items with the greatest weight from PCA. Components of functional interference changed over time in this sample. Change in these components could be due to treatment response. Further research is needed to examine this more closely. Cancer clusters are dynamic constructs and further studies are required to determine their validity and reliability.

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Table 1

Characteristics of Patients Eligible for RTOG 9714

Characteristic	(n=909)	
Age		
Median (years)	67	
Range	37 – 92	
	n	%
Treatment Arm		
8 Gy	460	51
30 Gy	449	49
Marital Status		
Partner	529	59
No partner	314	35
Not reported	66	6
Gender		
Male	448	49
Female	461	51
Race/Ethnicity		
White	654	72
Black	142	16
Hispanic	40	4
Other	18	2
Not reported	55	6
KPS		
40 – 60	212	23
70 – 80	489	54
90 – 100	205	23
Not reported	3	<1
Receiving bisphosphonates		
Yes	221	24
No	688	76
Painful sites		
Solitary	517	57
Multiple	392	43
Treatment site		
Weight bearing	506	56
Non-weight bearing	403	44
BPI Worst Pain Score		
<5	25	3
5 – 6	229	25
7 – 10	655	72

Table 2

Distribution of baseline BPI worst pain and functional item scores

Item	n	Mean ± SD	Median (min, max)
Worst pain	906	7.52±1.80	8 (0,10)
General Activity	894	6.39±3.01	7 (0,10)
Mood	896	5.15±3.25	5 (0,10)
Walking Ability	886	6.11±3.32	7 (0,10)
Normal Work	866	6.80±3.20	8 (0,10)
Relations with Others	891	3.79±3.28	3 (0,10)
Sleep	892	5.31±3.36	5 (0,10)
Enjoyment of Life	887	6.00±3.34	7 (0,10)

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Table 3

Spearman correlation amongst baseline worst pain and functional item scores

	Worst Pain	General Activity	Mood	Walking Ability	Normal Work	Relation with Others	Sleep	Enjoyment of life
Worst pain	1							
General Activity	0.46	1						
Mood	0.35	0.59	1					
Walking Ability	0.32	0.59	0.45	1				
Normal Work	0.37	0.69	0.50	0.62	1			
Relations with Others	0.28	0.41	0.62	0.36	0.43	1		
Sleep	0.32	0.39	0.46	0.28	0.37	0.42	1	
Enjoyment of Life	0.35	0.64	0.62	0.51	0.64	0.54	0.49	1

*P-value is <0.0001 between each item

Table 4

Principal components analysisBaseline factor loadings

Item	Physical Interference Cluster (Component 1)	Psychosocial Interference Cluster (Component 2)	Final Communality
Walking Ability	**0.85**	0.12	**0.74**
Normal Work	**0.83**	0.29	**0.78**
General Activity	0.75	0.41	0.73
Sleep	0.10	**0.78**	**0.62**
Relations with Others	0.26	**0.77**	**0.66**
Mood	0.40	0.74	0.71
Enjoyment of Life	0.56	0.62	0.70
Variance	58%	13%	
Cronbach's alpha	0.83	0.81	

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Table 5a

Functional Interference Clusters Responders

	Variance	Cronbach's alpha	Items
Baseline (all patients)			
Component 1	58%	0.83	normal work, walking ability
Component 2	13%	0.81	relations with others, sleep
Week 4			
Component 1	69%	0.91	normal work, walking ability, general activity, enjoyment of life
Component 2	9%	--	sleep
Week 8			
Component 1	70%	0.90	general activity, walking ability, normal work,
Component 2	9%	--	sleep
Week 12			
Component 1	73%	--	sleep
Component 2	8%	--	relations with others

* Principal components analysis with varimax rotation

Table 5b

Functional interference clusters Non-responders

	Variance	Cronbach's alpha	Items
Baseline (all patients)			
Component 1	58%	0.83	walking ability, normal work
Component 2	13%	0.81	relations with others, sleep
Week 4			
Component 1	64%	0.65	relations with others, sleep
Component 2	13%	--	walking ability
Week 8			
Component 1	59%	0.84	general activity, walking ability, normal work
Component 2	14%	--	sleep
Week 12			
Component 1	64%	0.81	walking ability, normal work
Component 2	11%	--	sleep

* Principal components analysis with varimax rotation

Table 6

Treatment Effect on Functional Item Scores

	Week 4 Treatment Response	Week 8 Treatment Response	Week 12 Treatment Response	Overall Trend**
		Spearman correlation*		
Physical interference component score (walking ability and normal work)	0.52	0.51	0.47	<0.0001
Psychosocial interference component score (sleep and relations with others)	0.49	0.45	0.46	<0.0001

* p-value is <0.0001 for each correlation.

** p-value from general linear mixed model, adjusting for time of assessment