

# Quality of life measurement in bone metastases: A literature review

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**Abstract:** Quality of life (QOL) has become an important consideration in the care of patients with bone metastases as prevalence, incidence and patient survival are on the rise. As a result, more interventional studies now measure patient's QOL as a meaningful endpoint. However, well-developed bone metastases specific quality of life instruments are lacking. A literature review was conducted to better understand the nature of QOL instruments used in bone metastases trials. A total of 47 articles evaluating QOL in patients with bone metastases were identified. Twenty-five different instruments were used to evaluate QOL with study-designed questionnaires and the EORTC QLQ-C30 being most commonly employed. Many studies used more than one scale or instrument to measure QOL. This makes it difficult to compare QOL in bone metastases patients across studies and come to any formal conclusions. Therefore, this review demonstrates the need to develop a bone module that can be used across countries in future clinical trials.

**Keywords:** bone metastases, quality of life, QOL instrument, review

## Introduction

Bone metastases are a significant cause of morbidity and skeletal complications in many cancer patients. Primary tumors of the breast and prostate are the most common to metastasize to the bone, with a post-mortem incidence of approximately 70% (Coleman 2006). Primary tumors of the lung, thyroid, and kidney also metastasize to the bone with a post-mortem incidence of approximately 30% to 40% (Perez et al 2004). The morbidity associated with metastatic bone diseases includes pain, hypercalcemia, pathological fractures, spinal instability, cord compression, and immobility (Manoso and Healey 2005).

Treatment options for bone metastases have expanded to include orthopedic interventions, newer generations of bisphosphonates and systemic therapy. With recent advances in effective treatment options and a multidisciplinary approach to cancer management, the survival of patients with bone metastases has increased. Consequently, an increasing number of people are living longer years with bone metastases and the need to maximize their quality of life (QOL) during these years is essential.

The World Health Organization defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (World Health Organization 1948). This multidimensional definition of health has encouraged health care professionals and clinical trials investigators to incorporate all aspects of health in treatment. Consequently, an increasing emphasis has been placed on QOL as an outcome measurement endpoint in clinical trials. Over the last three decades there has been an explosion of QOL studies in medical literature. A Medline search using "quality of life" as a keyword reveals a significant increase in the number of articles related to the topic over a period of 30 years, from 32 in 1973 to 5444 in 2004 (Siddiqui et al 2006).

Quality of life has become an important consideration in the management of bone metastases. QOL instruments help health care professionals to better understand the

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impact of new or existing treatments on various aspects of a patient's life. Recently, site-specific QOL instruments have been developed as the issues plaguing cancer patients differ depending on their symptoms, course of treatment and future outlook. However, bone metastases specific QOL instruments are lacking. The objective of this study was to review the QOL instruments that have been used in previous bone metastases trials.

## Methods

A literature review was conducted in July 2006 using Medline (PubMed) from OVID registries for any studies measuring QOL in patients with bone metastases from 1966 to June 2006. The keywords used were "bone neoplasms", "bone metastases" and "quality of life (QOL)". Studies involving a patient cohort with metastases sites other than the bone were excluded in hopes to better understand the specificity of instruments used in bone metastases trials alone. Any individual case reports, qualitative studies or review articles were also excluded.

## Results

Forty-seven trials measuring QOL in patients with bone metastases were identified. Table 1 presents the patient population number, treatment setting, and assessment tools in each study. Of the 47 studies, 18 included bisphosphonate treatments, 12 included surgical/orthopedic interventions, 8 involved radiotherapy and 9 investigated other treatment options for patients with bone metastases (Table 2). The 47 studies involved a total of 10,844 patients. The number of participants in the studies ranged from 7–1,171 with a median number 85.

A total of 24 different instruments were used to evaluate QOL including pain assessment scales, validated QOL instruments, and study-designed questionnaires (Table 3). The number of instruments used in each study varied. Excluding pain measurements other than the BPI or PPI, the number of instruments used to measure QOL ranged from 1 to 4. Of the 47 studies, 21 (45%), 17 (36%), 7 (15%), and 2 (4%) of the studies used 1, 2, 3, and 4 instruments, respectively. Most studies employed study-designed questionnaires ( $n = 10$ , 21%) or the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3 (EORTC QLQ-C30) ( $n = 10$ , 21%) as assessment tools.

## Summary of quality of life instruments employed

The EORTC QLQ-C30 is a validated questionnaire used to evaluate the quality of life of cancer patients. It consists of

30 questions incorporating five functional scales (physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health scale. The remaining items assess other symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation and diarrhea), as well as perceived financial difficulties associated with the disease and its treatment (Aaronson et al 1993). Ten out of the 47 studies used the EORTC QLQ-C30 (Kristensen et al 1999; Osoba et al 1999; DiLorenzo et al 2002; Smeland et al 2003; Body et al 2004; Collette et al 2004; Diel et al 2004; Jenlev et al 2005; Wardley et al 2005; Kaasa et al 2006). The EORTC QLQ-C30 is also supplemented by site-specific modules such as the BR 23 as used by Wardley and colleagues (2005). The BR23 consists of 23 breast cancer-specific questions focusing on the side effects of therapy, body image, sexuality and outlook for the future.

Study-designed assessments were used in 10 publications (van Holtzen-Verzantvoort et al 1991; van Holtzen-Verzantvoort et al 1993; Creswell 1995; van Holtzen-Verzantvoort et al 1996; Nair et al 1999; Osoba et al 1999; Schoeggl et al 2002; Hirabayashi et al 2003; van den Hout et al 2003; Anselmetti et al 2004). For example, Creswell and colleagues (1995) did not use the EORTC QLQ-C30 or any other established questionnaires but did design a disease-specific questionnaire addressing patients' perspectives on physical activity limitations and treatment expectations. This suggested the lack of a bone metastases-specific instrument. However, the use of a variety of study-designed assessments does not allow for outcome comparison between studies.

The Functional Assessment of Cancer Therapy-General questionnaire (FACT-G) is a multidimensional questionnaire developed and validated in cancer patients to measure the changes in the 4 main domains of the quality of life: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items) and functional well-being (7 items) (Cella et al 1993). As with the EORTC QLQ-C30, the FACT-G is also designed for cancer patients in general. The FACT-G was used to evaluate QOL in 5 articles (Vitale et al 2001; Saad et al 2002; Vogel et al 2004; Weinfurt et al 2004, 2005).

The Edmonton Symptom Assessment System (ESAS) is a validated 9-item, patient-rated, symptom verbal rating scale with domains in global pain, nausea, tiredness, depression, anxiety, drowsiness, appetite, sense of well-being, and shortness of breath (Bruera et al 1991). The ESAS was designed to assess the multidimensional nature of quality of life specific to palliative care and has been demonstrated to be valid and

**Table 1** Characteristics of bone metastases studies evaluating quality of life (QOL)

Author, Year Location	N	Treatment	QOL assessment tools	Performance assessment	Pain/Analgesic measurement	Other assessment tools	Number of instruments used to measure QOL
Anselmetti et al 2004 Italy	49	Orthopedic Intervention	Study designed: – Mobility (with or without aid) – Perform normal daily activities – Need to take NSAIDS or Opiates – Patient assessment of whether QOL changed after surgery		Y		1
Benevenia et al 2004 USA	20	Orthopedic Intervention	Allan Scoring System MSTS Aboulafia		Y		3
Body et al 2004 Europe, Russia, Kuwait, USA, Australia, New Zealand, South Africa	564	Bisphosphonate (Ibandronate)	EORTC QLQ-C30		Y		1
Callstrom et al 2002 USA	12	Efficacy of Radio-frequency ablation			Y-BPI		1
Cheung et al 2006 Canada	30	Orthopedic intervention	ESAS TFAS		Y		2
Chow et al 2004 Canada	15	Orthopedic Intervention	ESAS TFAS		Y		2
Clohisy et al 1997 USA	17	Evaluation of QOL Instrument	FLIC SF-36				2
Collette et al 2004 Belgium, Netherlands, Austria, Norway	391	Systemic therapy (Prednisone, Flutamide, Estramustine phosphate, Vinblastine) Radio-pharmaceutical therapy (Strontium-89 chloride) Radiotherapy	EORTC QLQ-C30	ECOG	Y		2
Cresswell 1995 UK	27	Bisphosphonate (Clodronate)	Study developed quality of life/ activity score	ECOG	Y		2
Di Lorenzo et al 2002 Italy, USA	75	Radiotherapy	EORTC QLQ-C30	ECOG	Y		2
Diel et al 2004 Europe, Kuwait, Russia, USA, South Africa	469	Bisphosphonate (Ibandronate)	EORTC QLQ-C30		Y	Survival	1
Ernst et al 2003 Canada	227	Bisphosphonate (Clodronate)	PROSQOLI		Y-PPI		2
Fernandez-Conde 1997 Spain	11	Bisphosphonate (Clodronate)		KPS	Y		1

(Continued)

Table 1 (Continued)

Author, Year Location	N	Treatment	QOL assessment tools	Performance assessment	Pain/Analgesic measurement	Other assessment tools	Number of instruments used to measure QOL
Gaze et al 1997 UK	245	Radiotherapy	Spitzer's QOL index HADS	ECOG/WHO	Y		3
Helwig 1997 Austria	19	Surgery		KPS			1
Hirabayashi et al 2003 Japan	81	Surgery	Study designed QOL parameter: Ambulation status Frankel neurologic functional classification				2
Jonler et al 2005 Denmark	917	Systemic treatment (Androgen-modulating therapy)	EORTC QLQ-C30				1
Kaasa et al 2006 Norway, Sweden	376	Radiotherapy	EORTC QLQ-C30 Fatigue questionnaire	KPS	Y		3
Kristensen et al 1999 Denmark	100	Bisphosphonate (Clodronate)	EORTC QLQ-C30 HADS	ECOG	Y		3
Lee et al 2000 Korea	38	Surgery		Physical Activity (Functional Classification of the New York Heart Association)	Y	Survival	1
Lipton et al 2000 USA, Canada, Australia, New Zealand	754	Bisphosphonate (Pamidronate)	Spitzer-quality of life index	ECOG	Y		2
Mancini et al 2004 Belgium	18	Bisphosphonate (Ibandronate)	ESAS	ECOG	Y		2
Nair 1999 India	31	Radiopharmaceutical therapy	Study-designed questionnaire: Mobility assessment scale		Y		1
Okuyama et al 1999 Japan	7	Surgery	Frankel neurologic functional classification	ECOG	Y		2
Osoba et al 1999 Canada	161	Systemic therapy	EORTC QLQ-C30 Study designed: QOLM-P14		Y-PPI		3
Pistevou-Gompaki et al 2004 Greece	24	Pain medication			Y-BPI		1
Popov et al 1997 Yugoslavia	15	Systemic	RSCL				1
Purohit et al 1994 UK	34	Bisphosphonate (Pamidronate)	RSCL		Y		1



Table 1 (Continued)

Author, Year Location	N	Treatment	QOL assessment tools	Performance assessment	Pain/Analgesic measurement	Other assessment tools	Number of instruments used to measure QOL
Vinholes et al 1997 UK	48	Bisphosphonate (Pamidronate)	RSCL	ECOG	Y		2
Vitale et al 2001 Italy	10	Bisphosphonate (Pamidronate)	FACT-G	ECOG	Y		2
Vogel et al 2004 USA	613	Bisphosphonate (Zoledronic Acid)	FACT-G		Y		1
Wai et al 2003 Canada	25	Surgery	ESAS TFAS				2
Walsh et al 1997 USA	61	Surgery	Frankel neurologic functional classification (modified)		Y		1
Wardley et al 2005 UK	101	Bisphosphonate (Zoledronic Acid)	EORTC QLQ-C30 and BR23	ECOG	Y		3
Weinfurt et al 2004 USA	1124	Bisphosphonate (Pamidronate, Zoledronic Acid)	FACT-G	ECOG			2
Weinfurt et al 2005 USA	248	Evaluation of SRE	FACT-G EQ-5D	ECOG	Y-BPI		4

**Abbreviations:** Y, yes; NSAIDS, nonsteroidal anti-inflammatory drugs; QOL, quality of life; MSTs, Musculoskeletal Tumor Society; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; BPI, Brief Pain Inventory; ESAS, Edmonton Symptom Assessment System; TFAS, Townsend Functional Assessment Scale; FLIC, Functional Living Index - Cancer; SF-36, Short Form-36; ECOG, Eastern Cooperative Oncology Group Performance Status; PROSQOL, Prostate Cancer-Specific Quality of Life Instrument; PPI, present pain intensity; KPS, Karnofsky Performance Status; HADS, Hospital Anxiety and Depression Scale; ECOG/WHO, Eastern Cooperative Oncology Group/World Health Organization performance status; QOLM-P14, Quality of Life Module - Prostate; RSCL, Rotterdam Symptom Checklist; EQ-5D, Euroqol Measure of Health Status; RTOG, Radiation Therapy Oncology Group; TESS, Toronto Extremity Salvage Score; GI, gastrointestinal; FACT-G, Functional Assessment of Cancer Therapy - General; BR23, European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire.

reliable in patients with terminal cancer (Bruera et al 1991). The ESAS was used in 4 of the articles (Wai et al 2003; Chow et al 2004; Mancini et al 2004; Cheung et al 2006).

The Rotterdam Symptom Checklist (RSCL), used in 4 of the articles (Purohit et al 1994; Popev et al 1997; Vinholes et al 1997; Steenland et al 1999), is a tool used to measure the psychological and physical distress in cancer patients. The RSCL consists of 38 items covering 3 domains: physical symptoms, psychological symptoms and activities of daily living (de Haes et al 1990).

The Brief Pain Inventory (BPI) evaluates patient's worst, average and current pain, analgesic consumption and the pain relief from medication. Pain interference with daily living is evaluated with questions concerning general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life (Cleeland and Ryan 1994). While the BPI is an excellent measure of pain intensity and interference, it is not a complete measurement of overall QOL and is often accompanied by other tools. Four articles in this review used the BPI to measure quality of life (Callstrom et al 2002; Saad et al 2002; Pisteveu-Gompaki et al 2004; Weinfurt et al 2005).

The EuroQol classification system (EQ-5D) is a generic health-related QOL instrument, designed for cost-utility analyses and comparisons of therapeutic effects across different diseases. The EQ-5D has five attributes (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (Brooks et al 2003). Three articles used the EQ-5D (Saad et al 2002; van den Hout et al 2003; Weinfurt et al 2005).

The Townsend Functional Assessment Scale (TFAS) is a classification of a patient's functional capabilities using four categories: normal pain-free function, normal function but with pain, significantly limited function requiring prostheses, and nonfunctional (Townsend et al 1994). Three articles used the TFAS (Wai et al 2003; Chow et al 2004; Cheung et al 2006).

The Frankel classification system was developed by the American Spinal Injury Association in spinal cord injuries (Frankel 1969). Three studies used the Frankel classification to measure neurological status of bone metastases patients in the surgery setting to categorize the degree of motor, sensory, and autonomic involvement (Hirabayashi et al 2001; Okuyama et al 1999; Walsh et al 1997).

The following instruments were used in two studies each:

The Functional Living Index: Cancer (FLIC) is a validated QOL instrument used to evaluate the effect of the symptoms of cancer and its treatment on functional ability in all areas of life (Schipper et al 1984). The Hospital Anxiety

**Table 2** Study treatment settings

Treatment	Number of studies
Bisphosphonates	18 (38%)
Surgical and orthopedic intervention	12 (26%)
Radiotherapy	8 (17%)
Other	9 (19%)
Systemic therapy	4 (9%)
Radiofrequency ablation	2 (4%)
Skeletal events evaluation	1 (2%)
Pain	1 (2%)
Total	47

and Depression Scale (HADS) consists of 14 statements relating to anxiety and depression based on patient experience over the past week (Zigmond and Snaith 1983). The Musculoskeletal Tumor Society (MSTS) functional assessment form measures functional outcomes in patients

**Table 3** Frequency of instruments used in clinical trials measuring quality of life in patients with bone metastases

Instrument	Frequency
ECOG (WHO) Performance Scores	15
Study-designed assessment	10
EORTC QLQ-C30	10
Functional Assessment of Cancer Therapy – General (FACT-G)	5
Rotterdam Symptom Checklist (RSCL)	4
Karnofsky Performance Score (KPS)	4
Edmonton Symptom Assessment Scale (ESAS)	4
Brief Pain Inventory (BPI)	4
EuroQol 5D (EQ-5D)	3
Townsend Functional Assessment Scale (TFAS)	3
Frankel Classification (Neurological status)	3
Functional Living Index: Cancer (FLIC)	2
Hospital Anxiety and Depression Scale (HADS)	2
MSTS	2
Present Pain Intensity scale (PPI)	2
SF-36	2
Spitzer's quality of life index	2
Abouafia Scoring System	1
Allan Scoring System	1
BR23	1
Fatigue Questionnaire	1
Physical Activity (Functional Classification of the New York Heart Association)	1
Prostate Cancer Specific Quality of Life Instrument (PROSQOLI)	1
Toronto Extremity Salvage Score (TESS)	1

with musculoskeletal tumors. The evaluation scores are determined by the restriction in activities (actual or prohibited) and the effect of these restrictions on the patient's lifestyle (Enneking 1987; Enneking et al 1993). The Short Form-36 (SF-36) is a validated generic tool used to evaluate overall health status in eight domains consisting of: physical functioning, role limitations secondary to physical problems, bodily pain, general health, vitality, social functioning, role limitations because of emotional problems and mental health (Ware 1993). The Spitzer's quality of life index has five items concerning activity, daily living, health, support and outlook each rates according the verbal description that most closely reflects the patient's status (Spitzer et al 1981). The Present Pain Intensity (PPI) is a six-point pain intensity scale of the McGill-Melzack Pain Questionnaire (Melzack 1975).

The following measurements were used in one study each:

The Toronto Extremity Salvage Score (TESS) evaluates physical disability in patients treated for extremity tumors. The TESS includes 30 items on activity limitations in daily life such as restrictions in body movement, mobility, self-care, and performance of daily tasks (Davis et al 1996). The Allan Scoring System is used to assess pain, independence and ambulation ability (Allan et al 1995). The Abouafia Scoring System scale is a scoring system for saddle reconstruction and is used to evaluate clinical function in patients post-operatively (Abouafia et al 1995). The fatigue questionnaire was developed for a hospital based study of chronic fatigue syndrome consisting of 11 items including domains such as physical and mental aspects of fatigue, duration of fatigue, percent of time the respondent felt fatigue, and muscle pain during rest and exercise (Kaasa et al 2006). The Prostate Cancer Specific Quality of Life Instrument (PROSQOLI) uses a series of nine linear analog scale related to pain, physical activity, fatigue, appetite, constipation, passing urine, family/marriage relationships, mood, and overall well being (Ernst et al 2003).

Other endpoints utilized especially in studies investigating bisphosphonates include the monitoring the occurrence of skeletal related events such as hypercalcemia, pathological fractures, spinal cord compression, use of surgery and radiation.

## Pain assessment

Thirty-nine of the studies measured the intensity and frequency of bony pain, its impact on function and physical activities, and analgesic consumption. Of the 8 studies that did not specifically evaluate pain, 6 utilized validated QOL instruments (EORTC QLQ-C30, FACT-G, FLIC, SF-36,

MSTS, TESS, ESAS, TFAS, RSCL), which include pain-related questions. Of the two remaining studies, one used a performance score while the other used an evaluation of neurological function and study-designed questionnaire evaluating ambulation.

## Performance evaluation

Forty-three percent of the studies ( $n = 20$ ) measured performance status in addition to QOL. The ECOG was the most commonly employed ( $n = 15$  [75%]), however the KPS was also used ( $n = 4$  [20%]). Lee and colleagues (2000) used the Functional Classification of the New York Heart Association to evaluate performance status and measure QOL. Helwig and colleagues (1997) utilized the KPS alone to evaluate QOL while Fernandez-conde and colleagues (1997) evaluated QOL using the KPS and monitoring analgesic consumption.

## Conclusion

Quality of life in patients with bone metastases is increasingly considered an essential outcome for clinical trials and patient management and therefore good assessment tools are of increasing importance. In recent years, a vast number of QOL instruments have been developed, including several instruments for the general cancer population. However, to date, none are specific to the problems associated with bone metastases.

Research in the field of bone metastases has focused on pain and its associated outcomes. However, QOL is affected by many factors other than pain, including limited mobility, reduced performance, side effects and impaired role functioning. Hence a wider range of end-points are required with greater sensitivity than those currently employed (Barton et al 2001).

From this review, there is increased evidence that an instrument incorporating pain from bone metastases along with other issues arising from skeletal complications as well as psychosocial domains is needed to improve the understanding of QOL in patients with bone metastases. Recently, Androver and colleagues (2005) developed a 35-item questionnaire using patient cohorts from different cancer centers in Spain. The domains identified were: pain, daily activities, mobility, energy/vitality, adjustment and coping, sexual activities, feelings, and health perception. However, this instrument has yet to be validated in different ethnic and cultural backgrounds. Another effort to develop a bone module across different countries that is coordinated by the EORTC-QLG is also currently underway.

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