Chapter 24
Quality of Life in Patients Suffering from Metastatic Skeletal Disease

Marko Popovic, Liang Zeng, and Edward Chow

Abstract Bone metastases are the most common manifestation of metastatic disease in advanced cancer patients. Health care professionals (HCPs) agree that maintenance or improvement in quality of life (QOL) is the main goal of palliative treatments for bone metastases. Historically, QOL was measured by generalized assessment tools. With advancement in treatments for bone metastases patients, there has been a need for the development of a bone metastases-specific QOL module. Recognizing this need, the European Organization for Research and Treatment of Cancer (EORTC) QOL Group developed the EORTC QLQ-BM22 (BM22). The BM22 is used to assess QOL in bone metastases patients in four domains: painful sites, pain characteristics, functional interference and psychosocial aspects. Input for the module came from both patients and HCPs from several countries with different cultures; the BM22 was subsequently subject to reliability and validity testing and the minimal clinically important differences of the module were explored. The Bone Metastases Quality of Life Questionnaire (BOMET-QOL) was also developed using input from HCPs and patients; however, unlike the BM22, the module has not been significantly validated cross-culturally. Notably, the module is shorter than the BM22 (10 vs. 22 items, respectively) and does not contain any specific QOL subscales that it assesses. Development of a third assessment module, the Functional Assessment of Cancer Therapy-Bone Pain (FACT-BP), involved solely input from patients. The 16 item FACT-BP is made up of three distinct subscales: general functioning, physical and bone pain and is shorter than the BM22. Investigators are encouraged to facilitate direct comparison between the three QOL assessment tools available for bone metastases patients which will allow HCPs to establish a globally standardized QOL module in this patient population.

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V. Vassiliou et al. (eds.), *Bone Metastases: A translational and Clinical Approach*,
Cancer Metastasis – Biology and Treatment 21, DOI 10.1007/978-94-007-7569-5_24,

Keywords Bone metastases • Quality of life • Advanced cancer • Palliative treatment

24.1 Introduction

Bone metastases are the most common manifestation of metastatic disease in advanced cancers, particularly in breast, prostate, and lung carcinomas [1]. Treatment of bone metastases involves localized therapies, such as external beam radiotherapy, as well as systemic interventions, including chemotherapy, hormonal therapy, and bisphosphonates. Management of bone metastases has become increasingly multidisciplinary in nature.

With advances in effective systemic treatment and supportive care, survival of patients with bone metastases has improved substantially. Certain subsets of patients with bone metastases (e.g. breast and prostate cancer with predominately bone or bone-only metastases) have life expectancies that range from 2 to 5 years [2]. Successful management of bone metastases during these years is essential for reducing skeletal complications and for maximizing patient quality of life (QOL). There have been clinical trials in various disciplines addressing the optimal management of bone metastases. As the survival of bone metastases patients increases, there is an greater need to accurately monitor the benefits and side effects of their treatment. Clinical trials have routinely included survival and tumour control as primary endpoints. As most treatments aim at relieving symptoms, palliative endpoints such as pain score, analgesic consumption, skeletal related events, and quality of life warrant inclusion as routine trial endpoints [3].

Over the last few years, QOL has seen a growing focus among professionals caring for this patient population. Presently, health care professionals (HCPs) agree that maintenance or improvement in QOL is the main goal of palliative treatments for bone metastases [4]. Thus, there exists a need for physicians, therapists, nurses, and others to stay updated on the evolving body of QOL-centred literature which remains a crucial consideration in deciding between various treatment regimens.

This chapter will discuss relevant quality of life issues in patients with bone metastases. Quality of life assessment will be thoroughly explored, with a particular emphasis on historical techniques as well as recent clinical trials outlining the development and validation of quality of life assessment modules in present use.

24.2 Overview of Historical Issues Concerning the Assessment of Quality of Life in Patients with Bone Metastases

The World Health Organization describes health as ‘not merely the absence of disease or infirmity, but a state of physical, mental and social well-being’ [5]. QOL is a subjective, multidimensional construct reflecting functional status, psychosocial well-being, health perceptions and disease- and treatment- related symptoms from the patient's perspective. It incorporates expectation, satisfaction, a value system among other aspects of a patient's life [6]. In palliative trials, as well as symptom control, QOL is a major endpoint. Since palliative interventions are unlikely to lead to survival prolongation and significant tumor regression, QOL is a more meaningful endpoint when compared with traditional endpoints such as survival times and local control. Quality of life issues are an important consideration for patients when making decisions for the treatment of bone metastases. More interventional studies now aim towards enhancing patients' QOL, often by reducing toxicity. In addition, regulatory bodies are giving increasing importance to QOL studies as an independent endpoint in determining the cost-effectiveness of competing therapies.

With advancement in systemic treatment of advanced cancer with osseous metastases (e.g. radiopharmaceuticals, bisphosphonates, chemotherapies, orthopedic interventions, and additional systemic treatments), there was, historically, more need than ever for the development of a QOL assessment tool specific to bone metastases patients in order for a comprehensive assessment of the benefits and side effects of these specific interventions [3].

Traditionally, patients with bone metastases in clinical trials have completed general QOL assessment tools. These instruments are generic for malignancy and not designed with the intent to cover key QOL issues relevant for cancer patients with bone metastases. Patients uniformly expressed that these instruments were not relevant for their situations as they did not thoroughly address the QOL issues related to the disease and the complications of bone metastases such as hypercalcaemia, pathological fractures, spinal cord compression, mobility and functional impairment of the diseased bone, nor the side effects of specific treatments.

There is general agreement that the patient is the most appropriate source of information regarding his/her QOL [7]. Only the patient can report their subjective experiences and priorities. Unfortunately, at the end of the twentieth century, there was a gap between theory and practice of QOL assessment in the clinical setting. It was been reported that 85 % of physicians felt patients are the best judge of their own QOL [8], yet definitions and measures of QOL were usually based, to a great extent, on the researchers' and clinicians' perception of what QOL issues are most relevant to their patients [9]. Many studies have shown that the agreement between patient and physician responses is poor and physician assessments are not appropriate as substitutes for self-assessment in palliative care. Furthermore, in a survey by Bezjak et al., 78 % of responding physicians acknowledged that when physicians and patients discuss QOL issues they may not be talking about the same thing [6].

Patients with bone metastases experience their own distinct symptoms and emotional issues when facing advanced cancer and its treatment. While pain is the most common symptom, it is not clear exactly which pain characteristics and patient characteristics influence the QOL of these patients [10]. Understanding the patient's perspective and how it compares to that of HCPs assists in recognizing the differences and develops management strategies better addressed to individual patient needs.

In a study by Detmar et al., almost all patients expressed a willingness to initiate and discuss the physical aspects of his or her disease [11]. On the other hand, 25 % of patients felt it was only appropriate to discuss emotional functioning at the initiative of their physician. An even greater reluctance was observed concerning the issues of social functioning and family life, with 28–36 % of patients waiting for the doctor to first raise the topic and another 20 % preferring not to hold a discussion on these issues at all. This suggests that patients may be uncertain about which issues are appropriate to discuss with their physician [11]. Physical issues such as symptoms from the disease or treatment may be thought of as the primary responsibility of the physician, while psychosocial problems, including 'worry' issues, seem to fall into a more private domain and patients may be uncomfortable bringing them up with HCPs.

Several physicians echo this position on the discussion of psychological issues. It was reported that physicians felt that discussion of the physical aspects of their patient's health was primarily their responsibility, while a number indicated that the discussion of psychosocial health problems should be shared with other HCPs [11]. In the case of emotional and social functioning, all physicians indicated that they generally defer the initiation of the topics to their patients [11]. Consequently, this miscommunication may hinder the discussion of psychosocial issues, which can lead to inaccurate diagnoses and inadequate treatment [12] as physicians tend to overlook problems or symptoms that are not obvious or mentioned explicitly by the patient [13].

24.2.1 Early Quality of Life Assessment in Bone Metastases Clinical Trials (1990–2005)

Before the introduction of bone metastases-specific QOL questionnaires, QOL as an outcome measure was increasingly being incorporated into trials that utilized general QOL assessment tools in the palliative care setting [14]. Five localized palliative radiotherapy trials for bony metastases were cited as of particular importance for examining QOL as an endpoint before QOL was widely explored in this patient population [14–18].

In a randomized trial comparing two fractionation schedules (10 Gy in a single fraction versus 22.5 Gy in five fractions) in 280 patients, Gaze et al. [17] assessed QOL and emotional status, and found no differences in these measures when comparing single to extended fractionation. The physicians in the study completed the Spitzer QOL index [19] according to the verbal description most closely reflecting the patient's status. The Spitzer index contains five items relating to activity, daily living, health, support and outlook, each rated from zero to two. The patients completed a Hospital Anxiety and Depression (HAD) questionnaire to assess clinically significant levels of anxiety and depression. Assessment occurred at baseline, at 1-week, and anywhere between 3 and 4 weeks after completion of radiotherapy and then at two monthly intervals. Of 216 patients assessed post treatment, the QOL and

HAD scores were available for 209 and 200, respectively. The study found no association between initial QOL parameters and the likelihood of achieving pain control. The prevalence of both anxiety and depression, as per the HAD scale, was reduced following treatment. The median HAD score was reduced from six pre-treatment to five after irradiation. The prevalence of definite (HAD score ≥ 11) and borderline (HAD score 7–10) anxiety and depression at baseline were 49 % and 39 %, respectively. After treatment, these levels had been reduced to 35 % and 32 %, respectively. The QOL as assessed by the Spitzer Index improved from a median pre-treatment score of six (range 0–10) to a median of seven (range 1–10) post radiotherapy. There was no difference in changes in HAD or QOL according to fractionation schedule. It must be noted that the physicians assessed QOL in this study; therefore, the possibility of over-estimation of post-treatment Spitzer scores existed. Nevertheless, there was a trend of improvement of patient self-rated anxiety and depression [17].

Nielsen et al. examined global QOL using the VAS (visual analogue scale) in a trial of a single 8 Gy versus 20 Gy in four fractions [15]. Two hundred and forty-one patients were enrolled in this trial. The patients completed the pain and global QOL evaluation forms on the first day of radiation treatment and then at clinic visits 4-, 8-, 12- and 20-weeks after treatment. The authors reported that there was no difference in the relative change in QOL at any stage between the two treatment arms. At 4-weeks, approximately 34 %, 20 %, and 11 % of patients in each arm achieved increases of greater than or equal to 25 %, 50 %, and 75 % respectively in their VAS QOL when compared to their pre-treatment status. However, the proportion of patients achieving complete well-being was only 7 % in each arm [15].

In the largest reported randomized prospective trial for the palliation of bone metastases comparing two fractionation schemes (1,157 patients evaluated), QOL assessment was one of several endpoints [16]. Steenland and colleagues used an extensive questionnaire comprising the Rotterdam Symptom Checklist [20] and the EORTC QLQ-C30 [21]. In addition, overall QOL was also measured using five EuroQOL questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The questionnaire (containing almost 60 questions) was filled out by the patients at baseline, then weekly for 3 months, and monthly for up to 2 years. The analysis of repeated measures showed that no statistically significant differences in overall QOL were observed between the two fractionation schedules ($p=0.22$) [16].

A single arm trial by Fossa et al. [18, 22] specifically examined the endpoint of QOL after palliative radiotherapy for men with hormone refractory prostate cancer. In this trial, 31 patients were treated with the radioisotope ^{89}Sr (strontium-89) and 106 received external beam radiotherapy. Of the latter group, 24 patients with poor performance status were treated with single fraction hemi-body irradiation (HBI) and the remainder with fractionated treatments to localized fields. Only 19 of 31 men treated with strontium-89 and 54 of the 106 men receiving external beam radiotherapy completed the 3-month questionnaire. The 73 patients who completed the questionnaire reported slight pain relief, with their mean scores decreasing from 51 to 44.

This is not surprising given that only one patient in the strontium-89 arm and eight patients in the external beam radiotherapy arm had less than six hot spots on bone scan. In fact, two thirds of the study population had 20 or more hot spots. Three-months after radiotherapy, 20 of 57 evaluable patients had reduced their analgesic intake, 17 reported no change in dose and 20 had increased their analgesic requirement. Their global QOL was virtually unchanged, with a mean of 54 pre-treatment and of 52 at 3 months. Given the advanced disease in this study population, there were likely other sites of pain outside the irradiated fields. This may explain the lack of impact on QOL in this study.

A study by Chow et al. [14] was in keeping with the findings by Gaze et al. and Nielsen et al. [15, 17]. Chow et al. utilized the Edmonton Symptom Assessment System (ESAS) to evaluate QOL in their cohort. Other than global and index pain, there was statistically significant improvement in patient anxiety and sense of well-being with palliative radiotherapy. They found that there was a slight worsening of fatigue scores immediately after the delivery of radiotherapy in the entire cohort. Chow et al. noted that measures may be employed to overcome this transient period of worsening fatigue. However, further studies are required to correlate clinical significance with the statistical significance of the ESAS symptoms [14].

Most treatment interventions have associated side effects. It is vitally important to document if these interventions have an impact on QOL while attempting to palliate specific symptoms. Though external beam radiotherapy is a local treatment, studies have shown it can improve patient QOL as well [14].

24.2.2 QOL Issues in Patients and HCPs

It is generally accepted that the patient's perspective is the gold standard for the measurement of QOL and, as a result, they should be the primary source regarding what issues are included in a QOL assessment tool [9]. What one patient regards as a severe problem may be considered only minimal to another patient [13]. The relevance of each domain may vary according to the stage of illness, treatment, age and cultural background [9], which makes it important that a wide range of patients are interviewed in the development of any QOL instrument. If we are able to understand the patient's perspective of their illness, we can develop management strategies appropriate to their individual needs [23].

Health care professionals provide a more objective evaluation of the patients' problems and symptoms [13]. They tend to outline what is typical in any given situation [24]. Some feel that HCP assessments are more meaningful for determining clinical significance because patient improvements are evaluated on clinical parameters [25]. The HCPs' perspective is also important in the development of QOL instruments as they are responsible for the administration and incorporation of the tools into their everyday practice. Therefore, it is important that HCPs contribute to questionnaire development in terms of content and structure.

Quality of life research has proven that it is necessary and can be applied to the clinical setting. Results of QOL assessments have provided significant contributions to the approval of new chemotherapeutic agents and supportive care measures [26, 27]. The next step is moving it into the "patient's realm" [24] so that they can use this information to lead a healthier and more meaningful life. One suggestion is to have physicians sit down with patients and go through their QOL scores to identify potential changes since their last visit. Although this may be time-consuming, it would facilitate discussion [28] and would help physicians understand the patient's total environment so that they could better manage their treatment. In a study by Detmar et al., physicians who had access to patient QOL scores identified a greater percentage of patients with moderate-to-severe health problems than those that did not [28]. It is important to help the patient interpret the data and suggest how they can employ this information into their daily life, just as HCPs do with their disease and treatment information [23].

It is clear that patients and HCPs have different opinions on what the most important issues in QOL are for patients with bone metastases. It is important that HCPs recognize these differences in their clinical practice to better improve their understanding of the patient's situation and diagnostic capabilities. Although it may not be possible to alleviate patient worries and concerns in a population where the disease is essentially incurable, a simple discussion of these issues is very important to patients. It was suggested that ongoing developments of QOL instruments should aim at identifying issues that most affect patients' QOL experience and providing an objective assessment tool for HCPs to adopt into their everyday practice. Only through this, they say, can we hope to improve the chances that physicians and patients will use the generated QOL information effectively [23].

24.3 The Development of the Bone Metastases-Specific Quality of Life Module: The EORTC QLQ-BM22

For more than two decades, the European Organization for Research and Treatment of Cancer (EORTC) has cultivated a modular approach to the evaluation of QOL in cancer patients in clinical trials. This advancement in QOL assessment began with the development of the EORTC QLQ-C30 general questionnaire [21] and has since led to the development of several validated modules for specific cancer diagnoses. More recently, the EORTC QLQ-C15-PAL was developed from the C30 to accommodate palliative cancer patients—those with a low performance status and for whom a 30-item questionnaire would prove quite tiresome and challenging [29]. The module development process is highly specific and regulated by the EORTC Quality of Life Group. This process consists of four phases: Phase I: Generation of relevant QOL issues; Phase II: Operationalization; Phase III: Pretesting of the provisional module; and Phase IV: Large scale international field testing of the module [29].

The use of diverse QOL questionnaires in trials in the late 1990s and early 2000s indicated that there was a strong need for a comprehensive QOL assessment tool developed directly with bone metastases patients and their treating HCPs. Previous generalized questionnaires may not have properly addressed the specific conditions of the bone metastases population; in addition, these general questionnaires were often lengthy and therefore potentially burdensome for patients. These reasons were compelling to patients and HCPs who both wanted Phase I testing to commence on a bony metastases-specific quality of life questionnaire. In conjunction with the EORTC Quality of Life Group, a bone metastases-specific module, the EORTC QLQ-BM22 (BM22), was developed to supplement the generalized EORTC cancer module, the EORTC QLQ-C30 [21]. The BM22 was developed to address the prevalent, immediate need for a comprehensive QOL assessment tool for use in clinical trials and routine clinical assessment of bone metastases patients. In the initial phase of its development, it was noteworthy and evident that patients and HCPs presented a difference in perspective with respect to the most important issues for cancer patients with bone metastases [30].

Preliminary open-ended interviews with HCPs and bone metastases patients constituted the first step in the development of the BM22. Any issues relating to QOL of patients with any stage of bone metastases were recorded. HCPs from a variety of disciplines (i.e. radiation oncology, medical oncology, palliative care services, orthopaedic surgery, nursing, radiation therapy, pharmacy, and psychosocial-spiritual care) were consulted for the initial list of items. Likewise, patients with bone metastases from a wide spectrum of disease states and treatment clinics (i.e. receiving chemotherapy, radiation, orthopaedic services, pain management, and supportive care) were interviewed. Both populations were heterogeneous in nature in order to accurately assess which issues were most relevant across a variety of bone metastases treatments and prognoses.

Preliminary interviews with patients and HCPs generated a list of 61 items relevant to patients with bone metastases (Table 24.1). This list was formatted into a questionnaire and distributed to a new cohort of bone metastases patients and HCPs. A total of 413 patients (174 male and 239 female) and 152 HCPs were interviewed. The interviews took place at five cancer centres: Odette Cancer Centre (OCC), Toronto, Ontario, Canada; Princess Margaret Hospital (PMH), Toronto, Ontario, Canada; Tom Baker Cancer Centre (TBCC), Calgary, Alberta, Canada; Liverpool Hospital, Liverpool, New South Wales, Australia; and Charité Hospital (Universitätsmedizin Berlin), Berlin, Germany.

The extent to which patients experienced each of the 61 issues during the course of his or her illness was compared to how relevant HCPs felt each item was to bone metastases patients in terms of quality of life scores [(1) “not at all” to (4) “very much”]. Patients and HCPs had significantly different mean scores for all of the 61 items ($p < 0.0055$) except for the item “feel in control, positive and confident”, for which the mean scores were 3.07 and 3.10 respectively ($p = 0.2215$). In addition, the mean scores reported by HCPs were almost always higher than that of patients [30].

Both patients and HCPs were asked to list five to ten issues that affected bone metastases patients most profoundly (Table 24.2), Patients and HCPs agreed that four items affected bone metastases patients profoundly: “long-term (chronic) pain”, “difficulty carrying out usual daily tasks”, “able to perform self-care” and “able to perform role functioning”. However, the difference in ranking between the

Table 24.1 List of 61 quality of life issues rated for relevancy by bone metastases patients and health care professionals

Symptom	
1	Long-term (or chronic) pain
2	Short-term (or acute), severe pain
3	Pain at rest (i.e. when sitting)
4	Pain with activity (i.e. when walking)
5	Pain aggravation with movement or weight-bearing
6	Uncontrolled, unmanageable pain
7	Pain at night preventing sleep
8	Aches and stiffness
9	*Lack of energy*
10	Numbness
11	Tingling
12	Burning sensation
13	Postural problems
Function	
14	Limited movement due to pain
15	Difficulty planning activities outside the home
16	Difficulty travelling outside the home (i.e. using public transportation, driving, sitting in a car)
17	Difficulty in carrying out meaningful activity (including employment)
18	*Able to perform self-care*
19	Able to return to work promptly
20	*Difficulty carrying out usual daily tasks* (i.e. *grocery shopping*, *work outside the home*, *housework*)
21	Difficulty bending
22	Difficulty lifting
23	Difficulty standing up
24	Difficulty climbing stairs
25	Difficulty sitting
26	Difficulty lying in bed
27	Difficulty lying flat
28	Ability to have sex
Side effect from treatment of bone metastases	
29	Drowsiness
30	Confusion
31	Dizziness
Psychosocial	
32	*Able to perform role functioning* (*including domestic and family roles*)
33	*Feeling socially isolated*
34	Strengthened relationships with family/friends
35	*Have a clear*, *alert mind*
36	Feel in control, positive, and confident
37	Hope to live as long as possible
38	Reluctance to pain medication
39	Fear of addiction to pain medication
40	*Anxiety*

(continued)

Table 24.1 (continued)

41	Frustration
42	*Mood changes*
43	Emotional stress of diagnosis of advanced, incurable cancer
44	Increased focus on spiritual issues
45	Loss of interest in activities you normally enjoy
46	Loess of interest in sex
47	Worry about pain
48	Worry about suffering
49	Worry about loss of mobility compromising independence
50	Worry about becoming dependent on others
51	Worry about current health status
52	Worry about the future
53	Worry about becoming bed-bound
54	Worry about disease progression, deterioration in condition, and future complications
55	Worry about running out of medical treatments
56	Worry about hospitalization
57	Worry about ending days in a hospital or nursing home
58	Worry about death
Treatment expectation	
59	Hope for sustained pain relief (reduce pain for as long as possible)
60	Hope treatment will reduce pain as much as possible
Other issue	
61	*Financial burden due to the illness*

Issues in *italics* are in the EORTC QLQ-C30

two groups was substantial with respect to the somatic and psychosocial issues. Patients focused more on psychosocial items (four of ten items) and included three ‘worry’ issues within their top ten (“worry about becoming dependent on others”, “worry about loss of mobility compromising independence” and “worry about disease progression, deterioration in condition and future complications”). These issues ranked 20th, 22nd, and 16th respectively by HCPs. Instead, HCPs focused more on items respective to symptoms (seven of ten items) with an emphasis on issues relating to pain (seven of ten items). Overall, somatic issues received much lower rankings from patients than from HCPs [30].

In this study, HCPs tended to focus on issues relating to cancer pain when rating items for the module [30]. Cancer pain is a significant problem in the bone metastases population [1] and many of the HCPs interviewed are involved in its treatment. Unrelieved cancer pain can have a negative impact on patient QOL [31–37], but it is not necessarily the sole or the most significant influencer. Rustøen et al. found that pain characteristics only had a small impact on QOL, explaining just 8.6 % of the variance of QOL scores [10]. When physical and social functioning were added to the analysis, the explained variance increased to 28.4 %; depression seemed to have the most significant impact with an increase of 14–42.4 % explained variance [10]. Therefore, pain is a problem for patients with bone metastases but there are additional and more important issues to patients in terms of influencing QOL.

Table 24.2 Patient and health care professional top ten relevant quality of life issues in bone metastases patients

Rank	Issue	% Patients	Issue	% HCP
1	**Long-term (or chronic) *pain***	41.4	**Able to perform self-care**	62.1
2	**Difficulty carrying out usual daily tasks (grocery shopping work outside the home housework)**	39.7	Uncontrolled unmanageable *pain* not relieved by pain killers	61.0
3	*Worry* about becoming dependent on others	38.7	**Long-term (or chronic) *pain***	54.2
7	*Worry* about loss of mobility compromising independence	37.3	Short-term (or acute) severe *pain*	52.4
5	*Worry* about disease progression deterioration in condition and future complications	32.9	*Pain* at night preventing sleep	50.0
6	**Able to perform self-care**	32.6	Limited movement due to *pain*	46.9
7	Difficulty in carrying out meaningful activity (including employment)	32.1	*Pain* at rest (when sitting)	45.1
8	**Able to perform role functioning (including domestic and family roles)**	32.0	*Pain* with activity (when walking)	41.0
9	Financial burden due to the illness	24.3	**Able to perform role functioning (including domestic and family roles)**	39.3
10	Hope treatment will reduce *pain* as much as possible	23.6	**Difficulty carrying out usual daily tasks (grocery shopping work outside the home housework)**	35.9

Boldface represents items that patients and HCPs agree should be included in the top ten

In the care of bone metastases patients, HCPs are frequently involved in the management of cancer pain, which could explain why they felt it was such a significant problem. However, in terms of QOL, HCPs need to realize that psychosocial issues tend to have a larger impact [30].

After the data from the 61 items was gathered and the most relevant aspects of QOL were found, the 61 item list was truncated into a 22 question list and was subsequently operationalized and formatted in accordance with EORTC templates: questions were arranged for a week-long recall time; phrased in the "have you had" question format and measured on a 4-point Likert-like scale from (1) "not at all" to (4) "very much".

24.3.1 Phase III: Pretesting the BM22

The original English version of the BM22 was translated, using a rigorous translation process based on iterative forward-backward procedures into a multitude of languages, including Chinese, Danish, Dutch, French, German, Greek, Italian, Japanese, Norwegian, Spanish (European and South American), Swedish and Turkish.

Table 24.3 Issues included in the bone metastases quality of life questionnaire (EORTC QLQ-BM22)

Location of pain
1. Back
2. Leg(s) or hip(s)
3. Arm(s) or shoulder(s)
4. Chest or ribs
5. Buttocks
Pain characteristics
6. Constant pain
7. Intermittent pain
8. Pain not relieved by medications
Functional interference
9. Pain while lying down
10. Pain while sitting
11. Pain when trying to stand up
12. Pain while walking
13. Pain with activities such as bending or climbing stairs
14. Pain with strenuous activity
15. Pain interfered with your sleeping
16. Modify your daily activities
Psychosocial aspects
17. Felt isolated from those close to you
18. Worried about loss of mobility
19. Worried about becoming dependent on others
20. Worried about your health in the future
21. Felt hopeful your pain will get better
22. Felt positive about your health

Phase III tested the acceptability and relevance of the BM22 on 170 patients from nine countries [4]. Participating countries included Argentina, Australia, China (Hong Kong), Canada, Germany, Greece, the Netherlands, Spain and the United Kingdom. The majority of patients (68 %) were non-English speaking. Overall, there were 83 men (49 %) and 87 women (51 %). The median age was 60 years (range: 29–92). Median time from primary cancer diagnosis to diagnosis of bone metastases was 1 year (range: 0–21). Patients interviewed were from a variety of ages and primary cancer sites that were undergoing various therapies. Problems identified relating to the clarity and wording of certain items were considered when determining whether items needed to be added or deleted. This phase was especially important as it assessed whether the module items were comparable cross-culturally, mainly among non-English-speaking nations [4].

The BM22 (Table 24.3) was well received in all nine countries. Patients found the questionnaire easy to complete and relevant to their condition.

Following completion of Phase III, two changes were made to the questionnaire based on multiple patient concerns, resulting in the deletion of one psychosocial item and the division of one functional interference item into two [4]. The development process as well as the final questionnaire subsequently underwent review by the executive members of the EORTC QOL Module Development Committee and both were approved [4].

24.3.2 *Phase IV: Large Scale International Field Testing of the Module*

The final phase of development of the EORTC QLQ-BM22 was international field testing of the module [38]. Specifically, psychometric testing in terms of reliability, validity and sensitivity to change was conducted for the instrument. A total of 400 patients from seven different countries were accrued during this phase to examine the module's reliability and validity. The majority of the patients (72 %) completed both the core module and the BM22 in less than 15 min. Many of them (93 %) did not have a problem with the wording or phrasing of items, and did not find them difficult (89 %), confusing (91 %) or upsetting (94 %). Only 21 % of patients required help completing the questionnaires.

24.3.2.1 Reliability and Validity of the BM22

Factor analysis of the QLQ-BM22 confirmed the presence of four distinct scales (painful sites, painful characteristics, functional interference and psychosocial aspects) [38]. In internal consistency testing, Cronbach's alpha ranged from 0.67 to 0.94 at baseline, and from 0.70 to 0.93 at follow-up for the four scales [4]. Therefore, items within each scale highly correlated with one another compared with items of another scale. Test–retest analysis of the QLQ-BM22 in patients with stable bone metastases revealed that all four scales showed 'good' reliability (all intraclass correlations exceeded 0.80) [38]. Correlations between the scales on the QLQ-C30 and the QLQ-BM22 verified that those scales assessing similar aspects were correlated, and conversely those scales assessing distinct areas of QOL were not. The QLQ-BM22 therefore covers relevant QOL aspects in bone metastases patients that are not evaluated by the QLQ-C30. Validity of the QLQ-BM22 was further supported through the known group comparisons, where all four scales are able to discriminate between patients of a better performance status and those of a poorer performance status [4].

In a later study, Zeng et al. compared bone metastasis-specific QOL scores among patients who responded differently to radiotherapy by using the BM22 in conjunction with the C30 [39]. A total of 79 patients from the original 400 patient group who received palliative radiotherapy from six countries (Canada, Cyprus, Egypt, Brazil, India and France) were included. At baseline, patients who had a partial response, pain progression and an indeterminate response had comparable QOL scores [39]. However, when QOL scores for the same sample were taken at 1-month follow-up, patients who did not respond to radiotherapy reported significantly different scores than those that responded [39]. Three of four BM22 scales were significantly different among groups. Responders had lower scores for painful sites ($p < 0.0001$), painful characteristics ($p < 0.0001$) and functional interference ($p < 0.0001$). The psychosocial scale did not reach statistical significance and it was hypothesized that additional issues, not addressed by radiotherapy, may play a larger role in this scale. Overall, Zeng et al. were able to show that the BM22 was able to differentiate between patients who respond to treatment and patients who do not [39].

24.3.3 Minimal Clinically Important Differences of the BM22

An important consideration for QOL instruments is the minimal clinically important differences (MCID) of the tool. Traditionally, analysis of QOL differences between arms in clinical trials was conducted purely via statistical methods. Given large enough sample sizes, even minor differences may be statistically significant, but whether this is of clinical relevance is unknown. Therefore, early establishment of MCID is important to assist clinicians in adopting QOL instruments in their trials. Using two commonly applied methods (anchor and distribution based analyses) and data from the Phase IV BM22 validation study, Zeng et al. established the MCID of the BM22 [40]. It was found that three of four scales of the QLQ-BM22 (painful sites, painful characteristics and functional interferences) demonstrated statistically significant MCID for improvement; no BM22 subscales had statistically significant MCID for deterioration. Changes of at least 20.1 (95 % CI: 7.1–33.2), 30.5 (13.8–47.3), 19.6 (5.0–34.3) and 30.5 (9.0–52.0) in the painful sites, painful characteristics, functional interferences and pain scales, respectively, constituted clinical significance for improvement. In addition, it was noted that a clinically meaningful improvement requires a greater change in QOL than a meaningful deterioration for the QLQ-BM22. It should be noted that due to the relatively low sample size for patients that improved or deteriorated, these data should be interpreted with caution, as evidenced by the wide confidence intervals.

Generally, the authors noted that patients that improved, deteriorated or were stable reported QOL scores appropriate to such change [40]. On average, a mean decrease in symptom severity and improvement in functional scales was recorded in patients that improved while those that deteriorated reported the opposite [40]. The validity of the QLQ-BM22 alongside the C30 was therefore strengthened as the BM22 was able to discriminate between these two different groups.

24.3.4 Features of the BM22

The BM22 is used to assess QOL in advanced cancer patients suffering from bone metastases. It encompasses four general areas of well-being: painful sites, pain characteristics, functional interference and psychosocial aspects. Items on the BM22 are grouped according to the subscale assessed; however, they appear as 22 unrelated questions on the module. Items are all formatted as questions in which response options utilize a Likert scale (1–4 inclusive). Along with the core QLQ-C30 questionnaire, administration of the BM22 is 52 questions long (30 questions of the C30 in addition to the 22 questions of the BM22). Recall period of the BM22 is 7 days. 1–4 numerical scores are converted to a 0–100 scale; higher scores on the QLQ-BM22 represent worse QOL for the subscales of painful sites, painful characteristics and psychosocial aspects, whereas higher scores on the functional interference subscale equate to better functioning.

24.4 Other Instruments for Assessment of QOL in Patients with Bone Metastases

Although the BM22 is most rigorously validated and most commonly used assessment tool for the evaluation of QOL in patients with bone metastases, previous investigators have developed other instruments aimed at this patient population.

24.4.1 The BOMET-QOL: Development and Validation

The Bone Metastases Quality of Life Questionnaire (BOMET-QOL) was developed in three phases [41, 42]. The first phase was concerned with item generation. Similar to the development of the QLQ-BM22, this first phase included an extensive literature search to determine the main issues of the bone metastases population [42]. Fifteen health care professionals (ten oncologists, one haematologist and four urologists) and 15 patients also identified main issues they felt were associated with QOL for this population [42]. Phase two was the item selection phase and required health care professionals to score items according to their frequency, importance and clarity. A preliminary questionnaire consisting of 25 items was then devised and delivered to 92 patients. Patients who were diagnosed with primary lung, breast, prostate cancer or myeloma, who were over the age of 18 and who had an expected survival of at least 6 months were included in this part of development. Factorial analysis and Rasch modeling were conducted on these completed questionnaires and this resulted in 25 items that were identified as most relevant for patients with bone metastases. Eight dimensions were recognized, accounting for 73.2 % of total variability [41, 42]. In addition, the questionnaire showed internal consistency [42]. The final development phase of the BOMET-QOL was conducted as an observational study with 263 patients with bone metastases who had primary breast, prostate, lung cancer or myeloma [41]. About one third of these patients had undergone chemotherapy and approximately three quarters had received zoledronic acid in the months before they completed the questionnaire. 6.1 % of patients who completed the questionnaire were receiving chemotherapy at the time. This final development stage reduced the 25 items of the BOMET-QOL to 10 [41]. Reduction of the questionnaire occurred in two distinct parts. Part one consisted of factor analysis with varimax rotation of primary BOMET-QOL items [41]. Part two consisted of the resulting factors computed by the Rasch rating scale models [41]. Determination of the contribution of each item to the global health measure was determined by the infit and outfit statistics of the Rasch analysis. Those items whose infit or outfit value was greater than 1.3 were excluded from the questionnaire. Rasch analysis was continued until the questionnaire was reduced to 10 items [41].

24.4.1.1 Features of the BOMET-QOL

The BOMET-QOL module was developed with the goal of evaluating QOL in patients with bone metastases [41]. The module has not been developed with the intention of being coupled with a general cancer questionnaire; rather, developers of the module recommend that the assessment tool be combined with cancer-specific tools. The BOMET-QOL consists of only ten items and is therefore by itself much shorter than the BM22 (22 items). The BOMET-QOL uses a 0–4 Likert scale as response options. Recall period for the questionnaire is the past 7 days. All of the questions on the BOMET-QOL are unrelated and all items appear as statements. In addition, items within the BOMET-QOL are not grouped into subscales. Simple summation of the 0–4 scores is used to score the BOMET-QOL; these raw scores are then standardized on a scale from 0 to 100. Higher scores on the BOMET-QOL represent better QOL in bone metastases patients.

24.4.2 The FACT-BP: Development and Validation

In contrast to the BM22, the development process of the FACT-BP did not involve four distinct phases of development, such as that required by the EORTC [43]. Instead, the first part of development was the item-content validation of the FACT-BP which involved ten patients. Important feedback provided by these patients was used to determine if the bone pain questions were relevant and comprehensible [43]. The scale was then adjusted accordingly based on all input collected.

The second part of development of the FACT-BP was undertaken with the help of patient samples from two separate clinical trials [44, 45]. The two studies examined the efficacy of either zoledronic acid or ibandronate in patients with metastatic breast cancer and either progressive bone metastases or skeletal-related events. The first trial involved 31 patients who received intravenous zoledronic acid (4 mg every 4 weeks) for 12 weeks [44], while the second trial followed 30 patients who received oral ibandronate (50 mg daily) for 12 weeks [45]. Data collected from these 61 patients were used to evaluate the validity of the FACT-BP module.

24.4.2.1 Features of the FACT-BP

Like the QLQ-BM22 and the BOMET-QOL, the FACT-BP was developed with the purpose of measuring QOL in cancer patients with bone metastases. The FACT-BP is comprised of three distinct subscales: general functioning, physical and bone pain [4]. When coupled with the FACT-G, the FACT-BP is 43 items long (27 FACT-G items in addition to 16 FACT-BP items). The FACT-BP uses a 0–4 inclusive Likert scale; recall period of the questionnaire is 7 days [4]. Fifteen items are formatted as questions while one item is a statement on the questionnaire [4]. All items on the module are organized based on the subscale assessed. Simple summation of raw FACT-BP scores is used to score the FACT-BP, albeit with some items reversed. Higher scores on the FACT-BP indicate better QOL and less bone pain.

24.5 Closing Remarks

This chapter has outlined the trials and tribulations that have been encountered leading to the development of standardized outcome assessment tools for use in bone metastases clinical trials—from establishing meaningful pain response endpoints to balancing what patients and HCPs believed were the most relevant QOL issues to bone metastases patients and harmonization of these items into the three comprehensive bone metastases-specific QOL questionnaires that we have today: the EORTC QLQ-BM22, the FACT-BP and the BOMET-QOL.

Widespread use of the International Bone Metastases Consensus Endpoints and the EORTC QLQ-BM22, the FACT-BP and the BOMET-QOL for assessment of pain response and QOL will facilitate inter-study comparisons and reveal optimal systemic and localized bone metastases-specific treatments, tailored to the needs of the patient. We encourage investigators to use patient-based assessment of pain scores, analgesic consumption, health related QOL, as well as any other study-specific endpoint evaluation tools in future bone metastases clinical trials. Furthermore, direct comparison between the three QOL assessment tools available for bone metastases patients will allow HCPs to establish a globally standardized QOL module in this patient population.

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